This is a digital copy of a book that was preserved for generations on library shelves before it was carefully scanned by Google as part of a project to make the world's books discoverable online.

It has survived long enough for the copyright to expire and the book to enter the public domain. A public domain book is one that was never subject to copyright or whose legal copyright term has expired. Whether a book is in the public domain may vary country to country. Public domain books are our gateways to the past, representing a wealth of history, culture and knowledge that's often difficult to discover.

Marks, notations and other marginalia present in the original volume will appear in this file - a reminder of this book's long journey from the publisher to a library and finally to you.

Usage guidelines

Google is proud to partner with libraries to digitize public domain materials and make them widely accessible. Public domain books belong to the public and we are merely their custodians. Nevertheless, this work is expensive, so in order to keep providing this resource, we have taken steps to prevent abuse by commercial parties, including placing technical restrictions on automated querying.

We also ask that you:

+ *Make non-commercial use of the files* We designed Google Book Search for use by individuals, and we request that you use these files for personal, non-commercial purposes.

+ *Refrain from automated querying* Do not send automated queries of any sort to Google's system: If you are conducting research on machine translation, optical character recognition or other areas where access to a large amount of text is helpful, please contact us. We encourage the use of public domain materials for these purposes and may be able to help.

+ *Maintain attribution* The Google "watermark" you see on each file is essential for informing people about this project and helping them find additional materials through Google Book Search. Please do not remove it.

+ *Keep it legal* Whatever your use, remember that you are responsible for ensuring that what you are doing is legal. Do not assume that just because we believe a book is in the public domain for users in the United States, that the work is also in the public domain for users in other countries. Whether a book is still in copyright varies from country to country, and we can't offer guidance on whether any specific use of any specific book is allowed. Please do not assume that a book's appearance in Google Book Search means it can be used in any manner anywhere in the world. Copyright infringement liability can be quite severe.

About Google Book Search

Google's mission is to organize the world's information and to make it universally accessible and useful. Google Book Search helps readers discover the world's books while helping authors and publishers reach new audiences. You can search through the full text of this book on the web at `http://books.google.com/`

COUNTWAY LIBRARY
HC 28P7 S

1-10-16-10M

PRESENTED TO

The New York Academy of Medicine

By Author

19

BOSTON MEDICAL
JAN 6 - 1964
LIBRARY

t, 851

Ductless Gland Cell Control

By

ROBERT C. MOEHLIG, M. D.

1st Lieut. M. R. C.

Ductless Gland Cell Control

By e

ROBERT C. MOEHLIG, M. D.
1st Lieut. M. R. C.

from [illegible] S. S. [illegible]

11155.

January 1918

8109

TO
MY FRIEND AND TEACHER
DR. MAX BALLIN

DUCTLESS GLAND CELL CONTROL

In this day of exact knowledge, it is only natural that the medical profession is giving a large share of its attention to the still unsettled question of the functions of the ductless glands. How wide the field of activity is can be realized when the literature upon the subject is consulted. Illustrative of this is Biedl's monumental work, "Innere Sekretion," in which one hundred and forty-five pages are devoted to references alone. The interrelationship of the ductless glands makes it quite difficult to separate the individual functions and furthermore certain of the glands seem to exercise both a stimulating and inhibitory action. The wonderful influence the ductless glands have on growth and metabolism is shown in the disease, Cretinism. The influence of the thyroid gland on the nervous system is well illustrated in the latter disease and exophthalmic goiter.

Today we are able to recognize diseases due to slight deviations from the normal functioning, thus speaking well for the progress made in this incomplete work. Since Brown-Séquard's first conscious effort to utilize testicular extract for therapeutic purposes, and Berthold's experiments on capons in 1889 to determine the existence of internal secretions on the sex glands, many theories have been advanced to explain the individual functions of the ductless glands. We can date the real beginning of ductless gland research from 1855, when Thomas Addison described the syndrome which bears his name and ascribed it to changes in the suprarenal glands. Since then, facts have accumulated rapidly, and more so after the discovery that cretinism and myxedema were due to the absence or lack of thyroid activity.

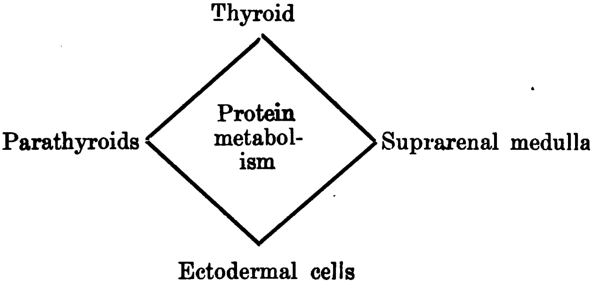
With the accumulation of facts, brought about by physiological and pathological research, has come likewise an accumulation of hypotheses so that it is with difficulty that logical conclusions can be drawn from them. It is clear, therefore, that we have not as yet reached the proper solution to the problem. A great part of the difficulty is due to the fact that the knowledge as to the chemistry of the internal secretions is still hazy and the physiological chemistry of the future, it is to be hoped, will clear up some of the more important doubtful points concerning their composition and function.

To add to this already over-filled list of hypotheses would hardly be justifiable unless such a hypothesis agreed in the main with the clinical and experimental facts which we possess. Some time ago it was thought that a solution to the problem might be found by studying the ductless gland system from an embryological standpoint. A rather brief article(1) was published on the subject, and since then several of the conclusions drawn have been confirmed experimentally. It was noted that hyper and hypofunctioning of some of the ductless glands resulted in more or less constant symptoms in certain tissues, depending upon their embryological origin. The action of the ductless gland must be specific and the truth of such a hypothesis can be readily ascertained, for hypo and hyperfunctioning must result in the production of clinical symptoms in the tissues controlled by the individual gland. It was found without exception that each and every time the thyroid and hypophysis were not functionating properly, the ectodermal and mesodermal tissues respectively were affected. On such a basis has the following article been written:

The thyroid mechanism, because of its importance and because to some extent the other ductless glands are dependent upon it, will receive consideration first. The thyroid mechanism, as will be assumed in this article, consists of the following:

1. The thyroid gland.
2. The parathyroids.
3. The suprarenal medulla.
4. The cells of ectodermal origin.
5. Protein metabolism.

It can be represented diagrammatically thus:



Naturally, the individual parts are definitely related to one another. The keystone of this mechanism is the thyroid gland and the other structures are more or less dependent upon its function and will share, therefore, in hypo and hyperfunctioning of the gland. Clinically, the state of the thyroid is reflected in the tissues of ectodermal origin.

The tissues derived from the ectoderm are as follows:

I. Skin.
II. Epidermal structures.
    (a) Hair.
    (b) Nails.
    (c) Glands.
        1. Sebaceous.
        2. Sudorifis.
        3. Salivary.
III. Corneal Epithelium.
IV. Lens of Eye.
V. Central Nervous System.
    (a) Nerves.
    (b) Ganglia.
VI. Eye, Optic Vesicle.
    (a) Optic Nerve.
    (b) Retina, etc.
VII. Olfactory Organ.
VIII. Auditory Organ.
IX. Lining of Mouth.
    (a) Teeth.
    (b) Hypophysis.
X. Anus.
XI. Chorion.
    (a) Placenta.
XII. Amnion.
    (a) Wolffian Duct.

Bearing out the theory, these tissues would give rise to clinical symptoms in dysfunctioning of the thyroid gland. An example of gross evidence of dysfunctioning is the condition known as cretinism. The most common changes in cretinism are as follows:

Skin and Epidermal Structures.—The skin is dry and inelastic, due to the lack of secretion from the sudorific and sebaceous glands. Chronic eczema and secondary pigmentation is common. The nails are striated, brittle and atrophic. Loss of hair, poor development of the hair, a bristly character and graying are also frequent findings.

Corneal Epithelium.—Hitschmann (2) in studying fifty-eight cretins, found conus, that is, a posterior staphyloma with a downward axis in five cases, which is a high percentage, as ordinarily this is found but twenty-seven times in a thousand cases. He remarks that the relationship this bears to the cretinic degeneration is entirely obscure. Conjunctivitides of different types is frequently seen. Parenchymatous keratitis is noted to be an accompanying symptom of myxedema. (3)

Lens of Eye.—Cataract and opacities of the lens are also a quite frequent finding.

Central Nervous System.—"The pathologico-anatomical findings in the brains of cretins are very diverse. In the majority of cases, the alterations of the brain structure are more or less of great intensity. Scholz and Zingerle found chronic meningitic alterations and a slight grade of hydrocephalus. Either the brain or the individual lobes may be smaller and frequently it is highly asymmetric. A juvenile type of brain is a frequent finding. Partaking of this under-development are the hemispheres, the brain-stem, cerebellum, etc. The number of convolutions are smaller or their number lessened. It is generally considered that the smallness of the cretin brain is primary while that of the skull secondary, such as Bourneville taught of idiots' brains. The inhibition of the development of the special sense organs is in part to be ascribed to lack of development in the central organs. The nervous status commonly shows increase of reflex as according to Scholz in fifty-two per cent; the field of vision was found by Ottolenghi to be restricted, especially outward and upward." (4)

The clinical symptoms that the lack of nervous development gives rise to are quite numerous. As can be judged from the pathologico-anatomical findings, the mental development is very low and on a par with a trained house dog. (Kocher) (5) Cretins are stupid, lacking in memory and decision. They can be trained to simple duties and are frequently called "beast men." Touch, pain and temperature-sense like the more highly specialized functions are greatly dulled. Hypothermism is the rule in these individuals. Constipation is a constant symptom in cretins. The heart sounds are weak, the pulse slow and feeble.

Olfactory and Auditory Organs.—The sense of smell is blunted. This is practically a constant symptom. Swelling of the mucosa of the nose is a frequent source of irritation. Cleveland (6) has called attention to the swellings on the turbinate bones, of waxy pallor, improved by thyroid treatment. As the olfactory organ is developed as part of the brain, the cause of the bluntness of smell can be readily explained. In countries in which cretinism is endemic, there are found a large number of deaf mutes. Thirty-two per cent of cretins are hard of hearing, according to Scholz.(7) As to the pathologico-anatomical findings, there is a diversity. Hammerschlag(8) found alterations in the peripheral hearing apparatus. There was also found an "incomplete ossification of the stapes, inhibition of development of the epithelial cells in the ductus cochlearis (Habermann,(9) Alexander),(10) shortening of the base of the skull, and thereby disturbance in the development of the organ of hearing. (Danzinger,(11) Bircher),(12) incomplete ossification of the organ of hearing with hyperostatic growths at other places. (Moos and Steinbrugge),(13) anomalies of the malleolus, (Nager),(14) myxedematous thickening of the tympanic mucous membrane, etc., have been regarded as the cause of the hardness of hearing. Recently E. Bircher(15) has strenuously criticized a portion of their findings or their significance." According to this hypothesis, however, as the auditory organ is a part of the ectoderm, it would show nutritional changes and would harmonize with the above findings. The sense of taste in cretins is quite markedly blunted.

Eye, Optic Vesicle.—Anomalies of sight are frequent. Use of the eye causes weariness. Neuroretinitis is occasionally found, improved by thyroid treatment. Interstitial keratitis has also been found. Less frequently there have been reported in this disease: sceleritis, keratitis, iritis, choroiditis, retinitis, with their various combinations. These conditions are more frequent in the allied condition, myxedema.

Lining of Mouth, Teeth, Hypophysis.—The mucous membrane of the mouth is pale, dry and inelastic. Quite striking is the development and changes found in the teeth. They appear late, are badly formed; there are frequent alterations in the structure; enamel development is defective; early caries, with hypoplasias and erosions, are the rule. Second dentition is rare. The milk teeth appear slowly and do not always fully develop, and thus rudiments of these teeth are seen in X-Ray pictures of these individuals. It is interesting to note the condition of the hypophysis. All are agreed that in hypoplastic conditions of the thyroid, alterations of the hypophysis are present. In endemic cretinism, the hypophysial changes are striking. Schoenemann(16) in his investigations found that in neighborhoods where goiter is endemic, strumous alterations are found frequently in the glandular part of the hypophysis. "Among one hundred and twelve cases, the hypophysis was normal in only twenty-seven. These persons did not have a goiter.

Among the cases with goiter, there was one in whom was found a hypophysis that could be regarded as probably normal" (Falta).(17) Biedl likewise quotes Schoenemann in regard to the hypophysis in this condition. The hypophysis is enlarged but degenerated. This is proven by the Roentgen ray plates. Ponfick(18) has found it to be completely atrophied. Boyce,(19) Biedl and others have found this state of the gland. Rogowitsch(20) has shown that thyroidectomy in adult rabbits results in an enlargement of the hypophysis in its glandular portion with vacuolization and degeneration of the protoplasmic cells. Such degenerative changes in the hypophysis should be expected theoretically since the hypophysis is of ectodermal origin and shares therefore in these nutritional changes.

Anus.—Swelling of the anus as mentioned by authors is quite a common feature.

One of the striking features in cretinism is the low stature and imperfect development of the genitals. The disturbances of bone growth in endemic and sporadic cretinism are similar in many respects. There is a noticeable delay in the closure of the epiphysis and a delay in the appearance of the bone nuclei. The ossification, as shown by numerous X-Ray plates, is striking. The delay in closure of the epiphysial structures is not always the same in all epiphyses, as shown by Breus and Kolisko.(21). The closure of the fontanelles is, as can be judged, also delayed. The fontanelle may still be open at the age of twenty or even later. In regard to thickness and length, the bones correspond to the relations of childhood (Falta). The circumference of the skulls is, on the other hand, not proportional to the rest of the bony growth, exceeding this and approaching more to a normal skull, although it does not correspond to the age of the individual. The zone of cartilage proliferation is diminished, the marrow cavity is narrowed, and the marrow spaces lessened.

To the above picture must be added the imperfect development of the genitals. In the female, the labia majora are underdeveloped, the uterus and ovaries are hypoplastic, and the breasts fail to develop. In the male, the penis is very small, cryptorchism is present, or the testicles descend later and are small. The pubic and axillary hairs are scanty. Boys at puberty fail to have the usual voice changes. The secondary sexual characteristics are therefore undeveloped.

The bone and sexual changes were purposely left to the last as these structures are of mesodermal origin. The explanation for the changes in the mesodermal tissues has been ascribed in this theory as due to the hypophysial degeneration. This will be fully discussed under the subject dealing with the hypophysial mechanism. As previously stated, the changes in the one gland often lead to changes in the other ductless glands, and care must be taken to make the proper distinctions between their individual actions. Since the bone marrow and lymphatic system are likewise of mesodermal origin, changes in the hematopoietic system must be looked for. This also will receive consideration.

The protein metabolism in cretinism is similar to all hypoplastic conditions of the thyroid. Scholz(22) found the metabolism at low ebb. Excretion of xanthin, creatinin, uric acid and sodium chloride were very slight, while ammonia and sulphuric acid were also very slowly excreted in amounts far below normal. Nitrogen-free substances are chiefly consumed. To summarize, then, protein metabolism is very much depressed.

While endemic cretinism was taken as an example of hypofunctioning of the thyroid, all conditions of this type show changes in the tissues of ectodermal origin. Attention has been called to the degenerative condition of the hypophysis, an ectodermal structure, together with the hypoplastic changes in the mesodermal tissues, the bone, genitalia, and hematopoietic system. In order to add clearness to the above remarks, it is now stated that the controlling factor of the mesodermal tissues is the hypophysial mechanism, of which the hypophysis is a part, and thus accounting for these changes. Naturally, this mechanism will receive full consideration later.

While endemic cretinism was selected as the representative disease of hypothyroidism, the changes noted are more or less characteristic of the latter condition in all its phases. Of course sporadic and endemic cretinism, athyreosis, infantile myxedema, etc., have certain distinguishing features, but on the whole it can be said that the ectodermal tissues are always affected in these diseases.

In the opposite condition, hyperthyroidism, the changes are also manifested in the ectodermal tissues. Exophthalmic goiter, or thyrotoxicosis, as some are wont to call it, is the disease brought to mind when hyperthyroidism is mentioned. The symptoms displayed in the ectodermal tissues are of an irritative type, and since the nutritional disturbances in the fixed tissues, *i.e.,* cornea, teeth, eye-grounds, etc., is not interfered with because of the increased metabolism, changes in these tissues are either absent or slight, the opposite, therefore, of hypothyroidism, in which metabolism is low.

Skin and Epidermal Structures.—Changes in the skin are many and varied. It is usually warm and moist. Sweating is at times excessive. Vasomotor flushes are common. Urticaria and dermographism is frequently present, as is vitiligo. More commonly, however, the skin has a brownish discoloration, ranging from pale to dark like sunburn, or similar to the diffuse pigmentation of Addison's disease. These latter changes are probably due to suprarenal medulla exhaustion. Alopecia is not uncommon, while early graying of the hair is said to occur. The nails are sometimes fissured. Interesting is the condition of the thymus. Capelle,(23) quoted by Falta, gives some interesting findings concerning this gland. According to him, forty-four per cent of exophthalmic goiter cases that died of intercurrent disease showed a hyperplasia of the thymus, eighty-two per cent of the cases that died of exophthalmic goiter itself, and almost one hundred per cent of these cases that died on operation.

Corneal Epithelium.—As previously stated, changes in a fixed structure such as the cornea are not to be expected in diseases of hyperfunctioning, as the nutrition is not markedly interfered with. However, ulceration of the cornea occurs, though not very frequently. It may be present in patients not severely ill and without exophthalmos, and not due, therefore, to undue exposure. The ulceration in the majority of cases must no doubt be ascribed to this undue exposure with exophthalmos.

Lens of the Eye.—"Patients with Basedow's disease bear cataract operations badly."—Möbius.(24)

Optic Nerve, Retina, etc.—Atrophy of the optic nerves occurs quite frequently and may be experimentally produced by the administration of thyroid gland extract. Adrenalin mydriasis can be produced experimentally. Miosis as well as other symptoms of sympathetic irritation occur quite often. Narrowing of the fields of vision has been noted, but Möbius(24) considers it the result of an associated hysteria. Amblyopia, achromatopsia, paralysis of various ocular muscles has been described, rather as complications, however, than as part of the main disease. In this relation, it is interesting to note that thyroid extract is being used in the treatment of malignant uveitis (Bordley).(25) Its beneficial effect can be explained through its action on the ectodermal tissues of which the uveal tract is a part.

Nervous System.—Osler(26) says concerning the nervous system, "The nervous system in Graves' disease is always abnormal, and in many patients it is the seat of the earliest symptoms. This is spoken of as 'nervousness,' and on closer inquiry appears often mental irritability, excitability, or restlessness. In severe acute cases there may be stupor or mania with confusion of ideas and hallucinations, either visual or auditory. Neuralgias sometimes occur in various parts of the body. Local twitchings may be annoying and also cramp, especially in the legs at night. A characteristic symptom of Graves' disease is tremor. It varies from a fine, barely perceptible tremor up to a distinct shaking of extremities, head or the whole body. Patients rarely fail to notice changes in the rate and rhythm of the heart-beat, and in many cases, palpitation or frequent pulse is mentioned as the earliest symptom. Attacks of vomiting sometimes occur, especially in severe cases. Diarrhea is a common symptom occurring in about one-third of the cases, sometimes in paroxysms or crises with or without vomiting." Rapid flow of ideas, terrifying dreams, hasty speech, changing moods, alteration of character, with fits of depression or unmotivated gaiety are often present in these individuals. Temporary insanity is quite frequently seen in exophthalmic patients. Likewise, psychic depression with thought of suicide.

Olfactory and Auditory Organs.—Hyperosmia and acuteness of hearing are quite a constant finding.

Lining of Mouth, Teeth, Hypophysis.—Hemorrhages into the mucous membranes are found in certain cases. Dental caries is occasionally found. The discussion on the corneal epithelium likewise applies to the teeth in this disease. We are more apt to see a dental caries in cases of long standing or of a very severe type, resulting in an exhaustion of the thyroid mechanism. In these cases also, we can find the explanation for myxedema following exophthalmic goiter. Very interesting, however, is the condition of the hypophysis. We should according to the theory expect a hyperplastic condition of this organ, and so we find it. The association of acromegaly and exophthalmic goiter is not at all rare. A thymus hyperplasia is also present quite constantly.

The following changes seen in exophthalmic goiter are considered in this theory as due to the hypophysial change. It is to be remembered that the hypophysial mechanism has under its control the mesodermal tissues, and hyperplastic conditions of the hypophysis will result in hyperfunctioning of the mesodermal tissues. In youthful individuals, changes in the *osseous system* occur frequently. Holmgren(27) has shown that there is an accelerated growth in height and a somewhat premature closure of the epiphysial junctures. Ballet(28) has reported a nineteen-year-old girl with Basedow's disease and gigantism (Falta). Alterations in the genitalia are quite pronounced at times. In men, there may be decrease of libido and impotence; in women, cessation of menstruation. Atrophy of the genitalia, both external and internal, are seen. The cause of the atrophy and sexual changes will be considered under the heading of the hypophysis and sexual gland relation.

Glycosuria, so frequently found in exophthalmic goiter, will also be discussed with the hypophysial mechanism. Falta(29) regards it as thyrogenic because of the fact that it comes on with the development of Basedow's disease and disappears again with its amelioration, and besides, after a cure of the disease, overloading tests show entirely normal relations. It is granted that the thyroid causes the glycosuria, but this is due to the stimulating action on the hypophysis. Of similar explanation is the hyperplasia of the lymphatic glands, spleen and blood changes (mononucleosis), as are the carbohydrate changes in hypo and hyperfunctioning of the thyroid.

How does the thyroid mechanism control these cells of ectodermal origin, if such is the case? This brings up the discussion of the individual parts of the mechanism. The antitoxic theory of thyroid function, which in the past attracted considerable attention, has practically been abandoned by present-day physiologists. It was first advanced by Notkin(30) and later taken up by F. Blum(31) who was a staunch advocate and did considerable work to prove the antitoxic function of the thyroid. He did not, however, consider the parathyroids in his theory, the removal of which we know results in tetany. The function as he considered it was to neutralize poisons derived from proteins in the intestine, called by him entertoxins. They are then locked up in the thyroid gland, and a by-product, thyreo-toxalbumin, is formed, which is later released from the thyroid as a harmless product. According to Blum, disturbances of the thyroid result because the thyreo-toxalbumin combined in the gland is released as such, brought about through some obstacle in its further neutralization.

When following insufficient thyroid secretion, there is a lack of sufficient union between the toxin and thyroid secretion; tetany, cachexia, myxedema and other similar conditions result. If the enterotoxin is still united, but not rapidly or sufficiently neutralized by the thyroid, then this condition results in certain types of goiter which are favorably influenced by iodide medication. On the other hand, if the combined thyreo-toxalbumin is thrown into the circulation, Blum assumes a partial insufficiency of the thyroid, resulting in Basedow's disease.

Biedl,(32) on the other hand, endeavors to disprove the theory on the ground that thyroid extract fed to myxedematous individuals and not, therefore, in combination with the thyroid cells of the individual, results in a cure. He, says Blum, himself, must admit that the thyroid secretion can, *per se,* be a cause of an intoxication. Furthermore, tetany resulting from parathyroidectomy receives but little attention from Blum and his followers, and this indeed is a great drawback to the theory.

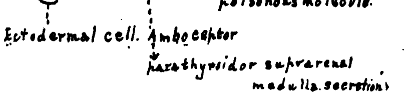
We must admit the ingenuity and novelty of the theory, but we cannot admit of its acceptance.

Today the absolute denial of an antitoxic function of the thyroid cannot be made as there are several good writers who maintain that such is its function. Reid Hunt,(33) of Washington, in his experiments, tries to prove that this gland protects us against injurious drugs. "When certain animals, such as rabbits, have been given aceto-nitril and thyroid preparations at the same time, they do not become poisoned; whereas, when they have taken the former alone, they do."—Lorand.(34) Biedl(35) says in answer to this that Reid Hunt himself admits that his experiments in no wise prove the antitoxic function of the thyroid, but may be the result of metabolic changes produced by the thyroid extract. Furthermore, this antitoxic function is not to be accepted, as it is exerted only against aceto-nitril and only to be proven in mice; and added to this is the fact that thyroid feeding in other animals and in mice does not protect them from poisoning but rather decreases their resistance, as for example, morphine. Perrin and Jeandelize(36) also assert that the resistance of thyroidectomized animals against arsenic is decreased. Biedl's argument in answer to Reid Hunt's experiments would hold good in the experiments of Breisacher(37) on thyroidectomized dogs, as well as those of the Japanese authority, Kishi,(38) who arrived at the conclusion that the thyroid has an antitoxic function, the experiments being made on one hundred and fifty thyroidectomized dogs, monkeys and other animals. This antitoxic function was also assumed by the writer in a previous article, to be sure, with no experimental facts of his own. A further study of this question has led to other conclusions. The purpose of this article is to show, if possible, that the secretions of the ductless glands exert a specific action on the body cells, depending upon their embryological origin. The experiments of research workers has made the task somewhat easier.

From certain facts which we have at hand, it seems reasonable to assume that the thyroid is a ductless gland, whose secretion contains iodine in the form of a nucleo-proteid and the function of which is to furnish a ferment or hormone which controls the rate of deamination of proteins. Kendall(39) of the Mayo clinic has furnished this hypothesis, stating that the function of the thyroid is to furnish a catalyzer which regulates the rate of deamination. Therefore, the more thyroid secretion, the more protein metabolism, and vice versa. He says, "The presence of the deaminizing catalyzer does not affect the mechanism of the formation of body proteins from foreign proteins, or the decomposition of body proteins into amino-acids. Woodyatt, from a study of chemical dissociation and the equilibrium existing in the body, has already suggested that the thyroid may be concerned with the dissociation of amino-acids or polypeptids derived from the breakdown of protein. It is obvious that during different periods of rest and activity, the organs require varying amounts of the iodin compound. We can, therefore, assume that the function of the thyroid is not only to elaborate this substance but also to supply the cells of the body with the amount necessary to meet the momentary demands of each cell. But, after cell activity has been heightened by an increase of the amount of iodin compound present, there must be some mechanism for the subsequent removal of some of the catalyzer from the cells and for carrying it back to the thyroid, there to be held again until again demanded. The vehicle for carrying the iodin compound from the gland is probably the colloid found in the thyroid secretion. It is suggested that the balance between free amino-acids and colloid may be the mechanism governing the supply and demand for the catalyzer substance. Previous investigators have produced hyperplasia in lower animals and fish by feeding a protein diet. The presence in the blood of abnormal amounts of amino-acids may be a stimulus to the activity of the thyroid." This latter suggestion was also made by the writer in the article previously referred to.

The thyroid, then, is the keystone to the mechanism. If it increases its function, the parathyroids and suprarenal medulla increase their function and this is manifested in the cells of ectodermal origin. And so it is in hypofunctioning. The function of the parathyroids and suprarenal medulla will now be considered and then the mechanism as a whole.

The functions of these two glands is to furnish a ferment which neutralizes the poisonous part of the protein molecule and in addition to this, to sensitize or hormonize, if you will, the cells of ectodermal origin. This latter action can be represented by the amboceptor group of Ehrlich, thus:



We attribute, therefore, a two-fold action to the parathyroids and suprarenal medulla. Vaughan(40) concludes that the poison in the protein molecule is the same in all true proteins, whether in pathogenic, non-pathogenic bacteria, in vegetable and animal proteins. Furthermore, that it is a split product of the protein molecule and it is neutralized by combination with non-poisonous groups; it exerts its poisonous action only when the proteins undergo molecular disruption. The parathyroids and suprarenal medulla's secretions would, according to this hypothesis, neutralize this poisonous molecule.

The antitoxic function will first be discussed, then the action on the cells of ectodermal origin. Vassale and Generali(41) were the first to advance the antitoxic function of the parathyroid. Pfeiffer and Meyer(42) endeavored to find the poisonous product in the blood stream resulting from parathyroidectomy. They were able to show that the blood of dogs with tetany had a stronger hemolytic action on that of guinea pigs than that of normal dogs. While the authors did not attribute any great importance to this, they did, however, lay great stress on the fact that the serum of dogs with tetany was toxic for partially parathyroidectomized mice and in some cases fatal to them. They believe that the specific poison is in the serum and is not excreted in the urine. Biedl,(43) from whom this is translated, does not think this of so great importance, but would consider that his experiment of venesection in a severe attack of tetany relieves it, and this continues for about twenty-four hours if fresh blood is injected, so that it may be interpreted that the fresh blood neutralizes the toxic product in the blood of the animal.

On the assumption that the tetany poison had an antigen character, Ceni and Besta(44) tried to recover specific antibodies following thyreoparathyroidectomy. They immunized rabbits and goats with serum from total ectomized dogs collected at the height of a tetanic attack and then took the immunized serum from these animals and injected it in doses ranging from nine to fifteen centimeters into ectomized dogs with severe tetany. They were able to demonstrate in practically all animals a rapid and sometimes immediate cessation of the acute phenomena, although the final outcome was in nowise altered. The authors claim that the therapeutic action of the immune serum is much more energetic, rapid and thorough than the treatment of antipyrine, recommended by Gley,(45) or the chloral hydrate treatment of Ughetti(46) and the bromide method of Canizzaro.(47) The authors were unable to prolong the life of a parathyroidectomized animal with their immune serum.

Berkeley and Beebe(48) believe that tetany is caused through some toxic product of metabolism. They were able to increase the symptoms of tetany by feeding meat and to increase the excretion of ammonia. In their estimation, the toxic substance is a protein product. They believe further that cases which are injected with ammonia or zanthin produce certain toxic symptoms, are improved by calcium and strontium salts, just as in tetany following parathyroidectomy. Frouin(49) found in thyro-parathyroidectomized animals an increase in the urinary output of ammonia and ammonium carbaminate, and believes tetany is due to this carbaminate poisoning. He was able to produce a typical tetany twenty-four to forty-eight hours after thyro-parathyroidectomy, with the injection of three to four grammes of sodium carbamate. Kendall,(50) in his article, says, "It is here suggested that the function of the parathyroid is to convert ammonium carbonate into urea." He is, therefore, perhaps unaware of Frouin's experiments.

Quite recently, Koch(51) through his experiments comes to the conclusion that methyl-cyanamid is the cause of tetany following parathyroidectomy, he having isolated this substance from the urine in parathyroidectomized dogs. His conclusions are that somewhere in the body methyl-cyanamid is generated. This substance has a physiologic use in animals. After parathyroidectomy, the substance accumulates in toxic quantities and is responsible for death of these animals. MacCallum(52) has made some interesting experiments to clear up the pathology of tetany. From these experiments, he believes that there exists a poison in parathyroidectomized animals which combines with certain cells of the central nervous system. He proved that the action was on the nerve cells and not upon the muscles by cutting the latter free from their nervous connections, and thereby confirming the earlier experiments of Lanz.

Ochsner(53) quoting Berkeley and Beebe, says, "These authors state, 'The nitrogen partitions in the urine in such patients (with tetany) are in most cases abnormal, with relatively high ammonia, high rest nitrogen, notable quantities of creatinin, but with diminished urea and creatinin excretion. Such findings indicate severe nutritional disturbance and the possibility of metabolic toxins being responsible for the symptoms in such cases is commonly accepted. The fact that under disturbed conditions of nitrogenous metabolism, a meat diet gives rise to metabolic products which may provoke convulsions, suggests that the meat diet has more than a passive rôle in producing the symptoms of parathyroid tetany.'" Throughout the literature on parathyroids is evidence to the effect that in their secretion rests some antitoxic function on certain protein products and the statement that the parathyroids are concerned in having an influence on the growth and nutrition of the body is justifiable.

An antitoxic function, similar to the parathyroids, has been assumed for the secretion of the suprarenal medulla. On what particular protein or proteins in the blood it exerts its antitoxic action has not as yet been determined. This suprarenal medulla secretion is epinephrin and is essential to life. Chemically, it is methylaminoethanol pyrocatechin and is thrown into the vena cava continuously. The blood of animals without suprarenals is poisonous. O. Schwarz(54) has shown that phloridzin injected into male rats following suprarenal extirpation results in toxic symptoms which are partially relieved by epinephrin. Furthermore, these rats show a reduction in the glycogen content and an increase in protein catabolism.

According to Brown-Séquard,(55) the blood of ectomized animals injected into animals of the same species, also ectomized, results in shortening the lives of the latter, while the blood of healthy animals prolongs it. Mariani(56) found a high toxicity in the urine of ectomized animals. No doubt the toxic substance is similar to that in parathyroidectomized animals. Mariani(56) claims that the blood-pressure raising principle of the suprarenal medulla is immediately destroyed by the blood of ectomized animals.

On the strength of these findings, plus the contribution of Soddu,(57) who found a beneficial influence through venesection and saline injections, the cause for this characteristic prostration and finally the death of suprarenalectomized animals has been laid to an accumulation of toxic metabolic products, especially in the musculature. These experiments are the foundation for the teaching that the function of the suprarenals is to neutralize toxic products of metabolism, the chemical nature of which is as yet unknown. This antitoxic function is also exerted, according to Charrin and Langlois,(58) on other poisons, such as nicotine or bacterial toxins. The above remarks concerning the antitoxic function is almost a literal translation from Biedl's work.

It has, however, been assumed that the function of the suprarenal medulla and cortex are entirely different, and that it is only the medullary portion which is concerned with the antitoxic function. As for the cortical portion, this shall receive consideration with the hypophysial mechanism. Dismissing for the present the antitoxic function of the parathyroids and suprarenal medulla, the action they have on the cells of ectodermal origin will now be studied. It is not reasonable to suppose that the parathyroids and suprarenal medulla sensitize the same set of cells. It has been concluded from a study of clinical, experimental, pathological and anatomical facts that the parathyroid secretion sensitizes all the cells of ectodermal origin with the great exception of the amyelinic or gray fibers of the nervous system. Under the latter head comes the sympathetic nervous system and the gray matter of the brain and spinal cord. These are sensitized by the secretion of the suprarenal medulla.

Hypo and hyperfunctioning of the parathyroids should, if the hypothesis is correct, give rise to symptoms in the tissues under their control, the typical and best known disease in which there is hypoparathyroidism or an entire absence of its secretion, will be discussed.

Strümpell(59) gives in brief the following symptomatology: "The paroxysm of tetany usually has certain prodromata consisting of slight general discomfort and pain and of a feeling of weakness and stiffness most marked in the arms. These symptoms last for some hours (at least) before the true convulsive stage begins. The extremities, and more particularly the fingers, almost always suffer first, and then after the arms, the lower extremities become involved. The spasm usually affects the toes first before it seizes upon the other parts of the leg. The symptoms are almost invariably bilateral and symmetrical. Other nervous symptoms in addition to cramps are but little pronounced in tetany. The most noticeable are paresthesia, tearing pains, etc. Anæsthesia occurs only rarely. There is no impairment of consciousness. In only a few cases has a combination of tetany and hallucinatory confusion been seen.

Optic neuritis has occasionally been observed. The comparative frequent formation of cataract in tetany is remarkable." If we remember that the myelinic gray fibers, the hair, the skin (in part), the nails, the ciliary epithelium, the lens of the eye, the optic nerve, the teeth (enamel), are of ectodermal origin and sensitized by the parathyroids, the above symptoms and those of chronic tetany, which are to be given, can easily be understood.

In chronic tetany, we are more apt to see the trophic disturbances as the following symptoms show: Increase in the electric excitability of the motor and sensory nerves is one of the most important features of the disease. Erb's, Chvostek's signs are present. During a tetany attack, parathyroidectomized dogs show an increase in temperature. This is also seen in human tetany. V. Jaksch(60) and v. Frankl-Hochwart(61) have noted especially that during the attack-free period, the temperature is often abnormally low. V. Jaksch(60) saw more or less fever in thirty-five observations in acute cases at the beginning of the disease.

Falta(62) in speaking of the trophic disturbances, says, "The trophic disturbances in tetany affect epithelial parts exclusively, the hair, nails, skin, enamel and ciliary epithelium." This was pointed out in the article(1) previously referred to. Rapid falling out of the hair is frequently seen. Adler and Thaler(63) found that this was a premonitory symptom of tetany. Walbaum(64) found cachexia appearing in rabbits with nutritional disturbances, especially roughening of their coats. Trichorrhexis was found by Speigler(65) in a case of chronic tetany. The nails become brittle and complete necrosis may occur, that may result in casting off of the nail. These disturbances last recounted (skin, nail, teeth, etc.) bring to mind cretinism, and this leaves no doubt that the thyroidparathyroid apparatus is involved.

The cataract in tetany develops very rapidly. Peters(66) began the first exact investigations on the subject. He showed that the cataract was produced by degenerative changes in the ciliary epithelium. In Erdheim's (67) experiments, he says, "In these cases (delayed death following parathyroidectomy), the tetany showed an outspoken chronic character. In addition, in these twelve animals there occurrred notable trophic disturbances, especially in the incisor teeth. Enamel defects showed themselves as white flakes on the normally yellow colored teeth. In addition, the teeth became brittle and gave rise to considerable pain if broken off within the alveolar process." Conjunctivitis is also very frequently observed in tetany. Falta(68) observed this regularly in parathyroidectomized dogs and cats. Skin ulcers are also often present. Naturally, since the thyroid disturbances are to be laid to pathology in the thyroid, the symptoms in the cells controlled by the parathyroids will not be as severe as if the primary pathology were in the parathyroids.

That the nervous symptoms are manifested in the myelinic fibers is evident from the anatomy. Strümpell(69) says, "The great myelinic mass of fibers, known as the pyramidal tract, is the chief one concerned in exciting voluntary movements that are executed with a definite purpose. Since movements of this nature—nearly all occupations and manual labors are performed far more frequently with the arms than with the legs—the part of the pyramidal tract intended for the upper extremity is accordingly much larger than that for the lower." From this latter fact, it can be understood why the spasms are severer in the upper extremities in human beings.

Furthermore, "Vassale and Donaggis found in the spinal cord of six parathyroidectomized dogs a microscopic alteration (after Mueller's fixation) which they considered a degeneration in the crossed pyramidal tracts identical in situation with that following ablation of the motor cortex and also a similar change in the posterior tracts. This apparent degeneration could not, however, be demonstrated microscopically with either the Marchi or the Weigert-Pal method. With a nigrosin stain the axis cylinders showed swelling and a granular appearance and the myelinic sheath showed atrophy and did not stain well.

Russell examined the brain and cord of seven dogs which died after tetany after parathyroid removal and found rather extensive chromatolysis, shrinkage and distortion of the pyramidal cells and increase in the number of neuroglia cells. He concluded that the anatomical alterations were sufficiently well marked to afford a basis for the functional changes which led to tetany. Edmund also found changes in the brain and cord of parathyroidectomized dogs. The Nissl bodies were no longer defined; chromatolysis was striking. Sometimes the substance took the stain deeply; in some cells the chromatophilous substance was absent. The changes are similar to those observed after acute poisoning."—Ochsner.(70)

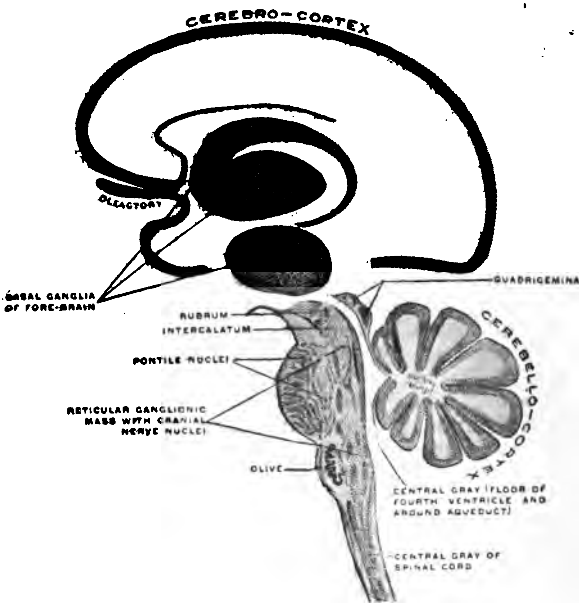
The skin proper and epidermal structures are sensitized, according to the hypothesis by the parathyroids. But the vasomotors, pilomotor and secretory systems of the skin are sensitized by the suprarenal medulla. This will be discussed later. The following is interesting in connection with the hypothesis that the myelinic fibers and skin are sensitized by the suprarenal medulla. This will be discussed later. The following is interesting in connection with the hypothesis that the myelinic fibers and skin are sensitized by the parathyroids. "Extraction of the fatty substance of the myelin sheath by boiling alcohol and ether brings out a fine network which resists trypsin digestion and termed *neurokeratin* on account of its resemblance to the keratin of epidermal structure."(71) It is perhaps more than a coincidence that the nucleo-proteid of the parathyroid secretion is not destroyed by the action of pepsin and hydrochloric acid in forty-eight hours.

Leaving for the present the parathyroids, the discussion of the sensitizing action of the suprarenal medulla on the amyelinic or gray fibers of the nervous system will now be undertaken. The suprarenal medulla is derived from the ectoderm and is developed as part of the sympathetic system. It secretes a substance termed "epinephrin" whose action has been conclusively proven to be the same as stimulation of the sympathetic. It has been assumed that this action is also exhibited on the gray matter of the brain and spinal cord. Gray's "Anatomy"(72) says: "The sympathetic system is not, as was so long taught, an independent system. It receives fibers from the cerebro-spinal system and arranges them for distribution to the splanchnic blood-vessels and the viscera. It receives fibers from the viscera and transmits fibers by way of the spinal nerves to unstriped muscles, to vessels, and to glands. It is simply an arrangement of spinal nerves to permit of the re-arrangement and transmission of impulses. In order to affect this, the spinal nerves are connected with a series of ganglia which possess a certain power of government or automatic action. In the sympathetic system amyelinic fibers predominate. The individual nerve-fibers are smaller in diameter than those of the cerebro-spinal sytem and the fibers are interrupted in gangliated plexuses and in the terminal ganglia. The majority but not all of the sympathetic fibers are found only in the sympathetic system." If, as has been assumed in this hypothesis, the suprarenal medulla secretion is exerted on the gray matter of the nervous system, then in hypoplastic conditions of the gland, a deficient development of these parts would be present.

Hypoplasia of the suprarenals has been found in hemicephaly and many other failures of brain development. Ziegler(73) cites several cases of hemicephaly, oxycephaly and anecephalous fetuses with hypoplasia of the suprarenals. Czerny(74) has seen absence of the medulla in five cases of hydrocephalous; Hansemann(75) eight cases of anecephalous with suprarenal atrophy. Wiesel(76) observed hypoplasia of the chromaffin system and hypoplasia of the vascular system and other changes. The following is a quotation from Kaufmann(77) showing the suprarenal bears to brain development, "Auch zu dem Grosshirn hat man die Nebenniere in funktionelle und genetische Beziehung gebracht Bei Hemicephalen und Anencephalen werden die Nebennieren *fast regelmässig* in grösserem oder geringerem Grade hypoplastisch gefunden. Nach Zander kommt die Nebennierenverkleinerung nur bei Defekten am vorderen Grosshirnteile vor. Oft bestehen hier gleichzeitig Misbildungen im Urogenitalsystem." This latter condition is not due to the suprarenal medulla failure but due to the loss of cortical substance. This question will receive consideration later.

From the following schematic representation can be seen those nervous structures sensitized by the suprarenal medulla. To this must be added the sympathetic nervous system as a whole and the posterior lobe of the hypophysis.

It would hardly be possible in this paper to discuss the individual functions of the gray masses, sensitized by the suprarenal medulla. Note, however, the action of the thalamus, "The thalamus is a ganglion interposed between the sensor tracts in the tegmentum and cerebral cortex, as well as an important link in the optic path. It also gives rise to motor tracts concerned with instinctive movements of an emotional nature. It is a relay station for the various tracts which convey sensations of touch, temperature, and pain from the body, extremities, head and neck, of muscle-sense, and of the special senses. It transmits these impulses to, and, reciprocally, receives impulses from the cerebrocortex. As an 'emotional' center, it is also under the inhibitory influence of the cerebral cortex, which, if the emotion be not too strong, prevents its external manifestations."(79)


CEREBRO-CORTEX
OLFACTORY
BASAL GANGLIA OF FORE-BRAIN
QUADRIGEMINA
RUBRUM
INTERCALATUM
PONTILE NUCLEI
RETICULAR GANGLIONIC MASS WITH CRANIAL NERVE NUCLEI
OLIVE
CEREBELLO-CORTEX
CENTRAL GRAY (FLOOR OF FOURTH VENTRICLE AND AROUND AQUEDUCT)
CENTRAL GRAY OF SPINAL CORD

The hypothesis is entirely in accord with these statements. It is to be remembered that some of the exciting causes of exophthalmic goiter are fright, grief, shock, sudden change in emotion, etc., and undoubtedly a causal relation exists between the action of the suprarenal medulla and thyroid, as has so often been asserted by various writers. The suprarenal medulla and its action of the thalamus will again be discussed with the sexual glands.

That the action of the suprarenal medulla secretion is on the olfactory bulb is strengthened by the fact that it is composed of amyelinic axoms with a neurilemma. Diminution of smell is the rule in myxedema and Addison's disease. "In tracing the various structures of the brain from the oblongata to the cerebral cortex, we follow anatomically what Nature has done in the evolution of the highest type of brain from that of the simplest and most ancient vertebræ. In the oblongata lie the centers which exert a very direct influence upon those of the entire cord. The striate bodies (caudatum, lenticula) and the thalami form a connecting link between the higher cerebral cortex and the oblongata and cord below. The extensive cerebral cortex, an aggregation of psychic centers, and therefore the seat of the will, controls the activities of the fore-brain ganglia (striatum, thalamus) and the cerebellar cortex, and these in turn preside over the functions of the lower centers, as in the way of motor responses to external impressions; such reactions may be delayed or immediate, according to the exercise of the will power residing in the cerebral cortex."(80)

Below is a summary of the gray masses in the brain, and these, it is to be remembered, are sensitized by the suprarenal medulla secretion. (Taken from Gray's "Anatomy.") (81)

I. Summary of Gray Masses in the Post Oblongata:

1. Central tubular gray (in "closed part").
2. Gray floor of fourth ventricle (in "open part").
3. Gliosa (of gelatinous Rolandi).
4. Nucleus funiculi gracilis.
5. Nucleus funiculi cuneatus.
6. Nucleus funiculi cuneati accessorius.
7. Nucleus lateralis.
8. Nucleus olivaris inferior.
9. Nucleus olivaris accessorius dorsalis.
10. Nucleus olivaris accessorius medialis.
11. Nucleus arcuatus.
12. Nucleus nervi hypoglossi.
13. Nucleus intercalatus.
14. Nucleus postremus.
15. Nucleus vagi (alæ cineræ).
16. Nucleus vestibularis (spinal division).
17. Nucleus funiculi teretis.
18. Nucleus ambiguus.
19. Nucleus tractus solitarii.
20. Nucleus tractus spinalis n. trigemini.
21. Formatio reticularis.

II. Summary of Gray Masses in the Pre-Oblongata:

1. Nucleus of Abducent Nerve.
2. Nucleus of Facial Nerve.
3. Afferent and Efferent Nucleus of Trigmenial Nerve.

4. Nucleus of Spinal Root of Trigeminal Nerve.
5. Nuclei of Acoustic Nerve— Cochlear Division.

Vestibular Division.

6. Superior Olivary Nucleus.
7. Nucleus of Trapezium.
8. Reticular Ganglionic Formation.
9. Nucleus Incertus.
10. Nucleus of Lateral Leminiscus.

III. Summary of Gray Masses in the Mid-Brain:

1. Central aqueduct gray,
    - (a) Oculomotor n. nucleus.
    - (b) Trochlear n. nucleus.
2. Nucleus radius descendentis nervi trigemini.
3. Nucleus of medial longitudinal bundle and post commissure.
4. Formatio reticularis.
5. Substantia nigra (intercalatum).
6. Rubrum (red nucleus).
7. Striatum cineureum pregemini.
8. Nucleus postgemini.
9. "Interpeduncular" ganglion.

What vital structures the suprarenal medulla secretion sensitizes and the grave symptoms produced by disease of the suprarenals can be readily understood. For example, the action on the cerebral cortex, the lack of suprarenal medulla secretion would theoretically result in symptoms manifested in the psychic centers, and so it is found clinically.

Hoskins(82) says, "On the whole it seems most likely that the characteristic asthenia of adrenal deficiency is due to loss of cortical tissue, whereas the medullary part has as its chief function the furnishing of a special stimulant to enable the body to cope with emergencies. In summary, we may say that the available evidence indicates that the adrenals secrete a substance, epinephrin, of remarkable potency. This substance selectively affects the tissues having sympathetic nervous control, thereby affecting many vital functions. Adrenal destruction results in fatal asthenia of the skeletal and cardiac muscle. This is probably due to loss of adrenal cortex, not epinephrin secreting tissue. Addision's disease is probably due, therefore, to functional failure of the adrenal cortex." The latter statement is to be questioned, as both medulla and cortex are affected, and are both, no doubt, concerned in its production. But that the asthenia in the skeletal muscles is due to loss of cortical substance is very probable. This question will be taken up with the discussion of the suprarenal cortex and the tissues derived from the mesothelium.

Addison's disease, in which the suprarenals are diseased, gives rise to the following symptoms: "In most cases, whether tuberculous or otherwise, the earliest symptom is an unusual tendency to fatigue on bodily or mental exertion."(83). This asthenia is shared by the skeletal muscles. The appetite may be capricious. There is a feeling of fullness after eating, nausea, eructations, and pyrosis. Constipation is the rule in the early stages, later irregular attacks of vomiting and diarrhea make their appearance.

Pigmentation.—The parts usually exposed to the light become intensely pigmented, the other portions are not so intense, but the areolæ, genitals, axillæ are quite pigmented. The color of the pigment varies. Areas of vitiligo may appear. The nail bed and nails are sometimes pigmented, and the hair seems to have a darker tint, looking dirty or dusty.

Nervous System.—Fatigue and constant apathy are common and is sometimes associated with depression, insomnia, or rarely increased tendency to sleep. Yawning is a marked symptom in some cases. Loss of memory, delirium, dizziness, tinnitus and muscalæ volitantes occur at times. Headache is frequent and sometimes violent.—Diminished sensibility or paresthesia—formication or numbness—sometimes exists in the pigmented or leukodermic areas.—Syncope comes on with alarming ease, with or without nausea or vomiting, and cold perspiration from exertion; a prolonged examination, a tubercular injection, and sometimes from accidental pressure on the abdomen. Weakness of the special senses, especially smell and hearing, are not uncommon. In some cases the mind is affected and imbecility may appear, and, in various degrees, dementia. The temperature is apt to be subnormal. These symptoms are manifested in the gray matter, under suprarenal medulla control. Notice also the similarity to the myxedematous characteristics.

Heart and Circulation.—Cardiac weakness is part of the picture of the disease. The heart beat and sounds are faint, the pulse small, soft, and usually slightly accelerated. Exertion is likely to bring on alarming dyspnea and palpitation. Atrophy of the heart is a constant finding.

Digestive Disturbances.—In the majority of cases there is more or less disturbance. In the later stages vomiting becomes severe and painful and hastens the fatal end.—Diarrhea is sometimes profuse and painful. Constipation is usually present in the earlier stages.

Genital Organs.—In reviewing the symptoms produced by this disease, it is seen that both ecto and mesodermal structures suffer. The medulla is derived from the ectoderm and sensitizes those tissues as stated, while the cortex is derived from the mesoderm and sensitizes, as will be shown later, the tissues derived from the mesothelium. A digression for a moment is perhaps pardonable, so that the part played by the cortex in Addison's disease will be more readily understood. The striated muscles, testicles, and ovaries are of mesothelial origin, and since the cortex, according to the hypothesis to be advanced, sensitizes these tissues, the asthenia in these muscles and the impotency of the male and amenorrhea of the female have a ready explanation. The medulla, therefore, has no part in producing these symptoms.

The fatigue, constant apathy, the association with depression, insomnia, loss of memory, delirium, loss of mind, dementia, and imbecility are explained by the lack of sensitizing action of the epinephrin on the cerebral cortex. Again the similarity to the mental condition of myxedema. Dementia præcox is often benefited by thyroid extract, producing an increase in action of the thyroid mechanism. The weakness of the special senses, especially smell and hearing, are also explained, as, for example, the lack of sensitizing epinephrin on the olfactory bulb decreases the sense of smell. The same applies to the *gray* nuclei of the glosso-pharyngeal and chorda-tympani nerves, in regard to taste, also the nuclei of the acoustic nerve in regard to the sense of hearing and tinnitus. Constipation in the earlier stages has the same explanation, while the diarrhea of later stages is due to the lack of sympathetic nerve control producing a relaxed sphincter.

The pigmentation produced in this disease deserves special attention. That it is due to lack of the suprarenal medulla secretion's action on certain protein products is perhaps the most reasonable explanation. Adami(84) says in regard to pigmentation: "French observers more particularly have called attention to the existence of oxidases within the living tissues, through whose actions proteins are darkened. It has, for example, been shown that the browning of the cut surface of an apple is due to this process. While similarly the conversion of the relatively colorless juice of certain Japanese plants into black lacquer by exposure to air has been found to be due to the presence of oxidases which act upon tyrosin and the aromatic products of protein decomposition. Experimentally, also, it can be shown that the action of strong acids upon protein produces a dark brown substance—'artificial melanin'—which is regarded as produced from the tryptophan, tyrosin and other aromatic bodies resulting from protein decomposition by the addition of oxygen.

Von Fürth would regard melanin and the melanoid bodies as developed by the action of intracellular oxidases (tyrosinase) upon the aromatic or chromogen groups of the proteid molecule. In favor of this view is the fact that a tyrosinase has been shown to be present in the ink-sacs of cuttle-fish, the pigment developed in these sacs, sepia, being allied in composition to melanin. And he would regard both the sulphur and iron as combined secondarily.

It is somewhat against this view that tyrosin is not one of the products gained from the decomposition of melanin, although indol and skatol are obtained. Indol, therefore, and the allied bodies, rather than tyrosin, would appear to be involved in the process. Independently, what would seem to be a striking support to this view has been adduced by W. L. Halle. He has demonstrated that, under the influence of an enzyme contained in the adrenal, that tyrosin is converted into adrenalin. We would point out that it is when the adrenal or its secretion is deficient that the characteristic pigmentation—bronzing—of Addison's disease shows itself. If the above view be correct, that pigments of the melanin group are of the nature of members of the aromatic series of derivatives of the protein molecule, then the bronzing gains its explanation, it is due to the want of conversion of the tyrosin and the allied bodies in the relative absence of the adrenals and their consequent accumulation in the tissues, and we would add that the greater darkening of the superficial parts most exposed to light and air of these aromatic bodies in these regions." In regard to this part of suprarenal function, Falta(85) says, "Probably the organism forms adrenalin from the aromatic split products of albumin, tyrosin and phenylalanin or oxyphenylserin."

It will be endeavored to prove that the action of epinephrin is exerted on the pigmented areas of the nervous system. The deeply staining pigmented nerve cells are found in the gray substance. Contrasting the white and gray matter, it is found that, "the white substance which forms about two-thirds of the neuraxis is the conducting substance, and its characteristic appearance is due to the *myelin sheath* which invest the axones in it. The *gray* substance is the sentient and reacting mass containing the cell bodies of the neurones. Its color is due to its translucency, its greater vascularity, and to a certain amount of *pigmented material in the cell elements.*"(86)

"Nerve-cell body—nerve cells fixed and stained by the methods of Nissl and Held show that the granule masses are 'stainable' (chromatophiles; tigroid bodies; Nissl bodies;) probably of the nature of a *nucleo-proteid* (MacCallum), and looked upon as a sort of a nutritive reserve. Many of the larger cells (found in the ventral horns of the spinal cord, in spinal ganglia, in large pyramidal layer of cerebral cortex, in Purkinjean cell layer of cerebellum and in the column of Clarke; (all sensitized according to the hypothesis by the suprarenal medulla), possess more or less *pigmented* material adjacent to the nucleus. The cells of the inter-calatum (substantia nigra) and locus cœrculeus contain an abundance of such pigment granules.—Nissl, after years of painstaking investigation, has classified nerve-cells into a great many different species in accordance with their reaction to staining agents. The cells are characterized by pigment (marked only in man), which varies from a pale brown in the young to an absolute black structure in the aged. (The suprarenal action is less in the aged.)—Those branches of the sympathetic which present a well-marked reddish-gray color are composed more especially of *amyelinic* axones intermixed with a few myelinic axones; while those of a white color contain more of the latter and a few of the former."(87) It must be understood, however, that in all situations, the action of the parathyroids and suprarenal medulla is specific, and exert their action only on their respective cells just as in those situations where myelinic and amyelinic fibers alone are present. The cerebro-spinal ganglia found on the dorsal root of each spinal nerve, on the glosso-pharyngeal and vagus nerves, and forming the gangliated cord of the sympathetic, is seen to consist of a reddish-gray substance.

Concerning the layer of small and larger pyramidal cortical cells, Gray's "Anatomy"(88) says in part: "It (pyramidal cell) contains granular pigment and stains deeply with ordinary agents. And the rubrum, so termed from its reddish tinge in the fresh brain, which it owes to the pigmentation of its cells as well as to its greater vascularity." In the pregeniculum, the nerve cells in the gray substance are large, multipolar and pigmented. The olfactory bulb is of a reddish-gray color.

Theoretically, changes in these cells and pigment should be evident after stimulation or exercise of these gray pigmented areas. Experiments have abundantly proven that there are such changes. Crile(89) has found such changes in his experiments on emotion. It was previously noted that the Nissl bodies were probably in the nature of a nucleo-proteid, and fatigue experiments have shown a disintegration of these bodies following exercise. This action is probably brought about by the action of the suprarenal medulla secretion.

The action of epinephrin on the eye is as follows: It causes a dilatation of the pupil, retraction of the nictating membrane and eye-lids, and protrusion of the eye-balls. This last action is interesting in connection with the exophthalmus of exophthalmic goiter. Many writers have concluded that the disease was due to an affection of the sympathetic system. This alone, however, cannot satisfactorily explain the disease. It is, undoubtedly, the action of the sympathetic which causes the exophthalmus. Such, also, is the conclusion of the Mayo Brothers.(90) There is in exophthalmic goiter an increased function of the suprarenal medulla, and this is manifested in those parts controlled by the gray masses and amyelinic fibers. Attention has previously been called to the fact that there are anatomical changes in the nervous system in cretins and myxedematous individuals, consisting of destruction of nervous cells, and nervous processes, *chromatolysis* and augmentation of neuroglia.

Crile(91) in his article "Kinetic Drive," states that the brain, thyroid and suprarenals are definitely related. He says: "In this interrelation of the brain, the thyroid and the suprarenals, we have what, perhaps, is the master key to automatic action of the body, that is through the special senses environmental stimuli reach the brain and cause it to liberate energy, which in turn activates certain other organs and tissues, among which are the thyroid and suprarenals. The increased output of thyroideiodin, by facilitating the transmission of electric currents through semipermeable membranes, increases the passage of nerve impulses and sets pace for energy conversion. In consequence, the suprarenals are driven to increased activity, and the increased adrenin in turn excites the brain to still greater activity, the results of which are equivalent to increased work of the sympathetic nervous system. These results are principally the following: increased heart beat, increased respiration, raised blood pressure, increased sweating thirst, the transfer of much of the blood from the splanchnic area to the surface, increased output of glycogen, increased power of the muscles to metabolize glycogen, increased acid excretion in the urine, certain histologic and chemical changes and exhaustion."

The modus operandi of epinephrin on the tissues is still in doubt. The experiments of Straub(92) and Kretschmer(93) bring some interesting facts to light, and, furthermore, tend to show the physiological action of the epinephrin in the system. The conclusions drawn from the experiments were, according to Straub:

"1. Poison, which is already incorporated in the specifically affected cells, is impotent.
2. Poison, that is not incorporated, is likewise impotent.
3. But the poisonous action is present only during and throughout that period where the poison is being incorporated into the cells."

The amboceptor hypothesis as advanced in this article is in agreement with these conclusions. The sensitization action of the suprarenal medulla secretion is perhaps active during the time it is being incorporated in the cells and at the same time the poisonous molecule of the proteid is being neutralized.

The hypophysial mechanism and the relation of the thyroid mechanism to it will be discussed later. Suffice to say for the present that the hypophysial mechanism consisting of the anterior and posterior lobe of the hypophysis and the suprarenal cortex has under its control carbohydrate and fat metabolism and the cells of mesodermal origin. The hypophysis is an ectodermal structure and theoretically sensitized by the parathyroids and suprarenal medulla. In reference to its embryology, Gray's "Anatomy"(94) says: "The hypophysis is a structure of twofold origin, giving rise to a division into a prehypophysis and a posthypophysis. The posthypophysis alone is of neural origin, developing as a neutral diverticulum, from the primitive neural tube. The prehypophysis develops from the stomadæum, or primitive buccal cavity, as a tubular diverticulum (Rathke's), which eventually loses its connection with the oral tissues to become included within the cranial cavity and intimately attached to the neural bud. Both pre- and posthypophysis are therefore of ectodermal origin and have developed from a conjunction of surface tissues which have migrated from opposed (ventral and dorsal) parts through the head! The prehypophysis is much the larger and somewhat embraces the posthypophysis; the two are inseparable, however, and together occupy the fossa hypophysis of the sphenoid. The two parts of the hypophysis are as distinct in structure as they are in embryonic origin. The posthypophysis consists of a mass of neuroglia, connective tissue, and bloodvessels: the structures of the prehypophysis is distinctly glandular, resembling that of the parathyroid bodies. The tuber is a thin-walled conical projection in the intercrural space cephalad of the albicantia. Its apical portion is attentuated to form the stalk of the hypophysis; this is generally termed the infundibulum, while the cavity of the funnel-shaped diverticulum is called the infundibular recess of the third ventricle. The gray lamina composing the tuber is continuous with the central ventricular gray and, therefore, with the terma."

It has been assumed from the facts at hand that the action of the parathyroids is on the prehypophysis or anterior lobe, while the suprarenal medulla's action is on the posthypophysis or posterior lobe. While for the present all the reasons for this assumption will not be given, as it would only serve to detract the reader from the issue, nevertheless it can be understood from the above why epinephrin may cause glycosuria, i. e., its action has a stimulating effect on the posthypophysis which is concerned in carbohydrate metabolism. And, likewise, why thyroid extract frequently causes glycosuria.

It is to be especially noted that there is present in the posthypophysis a certain amount of chromaffin tissue. Kaufmann(95) says: "Unter den Zellen des drüsigen Teils hat man groze chromaphile Zellen (Flesch) unter denen man nach Schoenemann bei Hämalaum—Eösinförbung rot oder blau gefärote eosin und Cyanophile—oder auch acido kleine weist, unscharf, begrenzteile, Zellen, Steedt's Hauptzellen unterscheiden."

Furthermore, there seems to be evidence that the pituitary contains epinephrin as shown by the following: "Pituitary extracts when prepared by certain methods," Watanabe and Crawford(96) state, "yield color reactions which would suggest the presence of epinephrin or an epinephrin-like compound, and the physiologic actions of such solutions can be explained by the presence of such a compound, but modified by admixed substances. Epinephrin has not been isolated from these glands, and this may be due to the small amounts present which would not be precipitated by the method now used for obtaining epinephrin."

It has been noted that cataract formation and optic neuritis are of frequent occurrence in tetany, while the special sense of sight is not particularly affected in Addison's disease. This is due to lack of parathyroid action. It is seen that the optic nerve has a special development. "Optic vesicles appear as two diverticulum, each budding from either side of the primary forebrain vesicle, their distal ends growing considerably and coming into contact with the overlying epidermis while the proximal or attached ends assume a stalk-like shape. The distal sac-like end becomes invaginated and forms the retina of the eye, while the stalk upon obliteration of its cavity forms the optic nerve. It is necessary to state here that as development proceeds, the optic stalk becomes relatively shifted caudad and forms more intimate connections with the thalamus and mid-brain." (Strümpell).(97) The fibers of each tract pass by way of the pulvinar of the optic thalamus, the external corpus geniculatum and the anterior corpus quadragemina to the cortex of the occipital lobe.

Disturbances of vision are found most constantly in diseases of the cuneus, particularly of the cortex about the calcarine fissure and the first occipital convolution. In this region the sensations of light as such, seem therefore to take their rise. The parathyroids sensitize this white optic nerve. In this regard may be mentioned the following from Gray's "Anatomy."(98) "Special Types of Gray's Substance."

1. *The Occipital Lobe.*—In the cuneus and the calcarine fissure, the occipital lobe, Cajal has recently described as many as nine layers. Here the inner band of Baillarger is absent; the outer band of Baillarger or band of Gennari is, on the other hand, of considerable thickness.—In the layer of small pyramidal cells, fusiform cells identical with the above are seen as well as ovoid or star-like elements with the ascending axones, the cells of Martinotti. Those of the cortex form the visual center, and it has been shown by Dr. J. S. Bolton that in old-standing cases of optic atrophy the thickness of Gennari's band is reduced nearly fifty per cent.

To show that the band of Gennari is of white substance, and therefore sensitized by the parathyroids, the following extract is quoted: "An alteration of gray and white stripes is discernible, particularly in the occipital cortex, where a *white* band runs parallel with the cortical surface between two gray strata; this white stripe first described by Gennari, and usually bearing his name, is also called the band of Vicq d'Axyr."(99) It must not be forgotten, however, that parts of the eye proper are sensitized by the suprarenal medulla, viz., the retina, iris, choroid.

Since the hypophysis is of ectodermal origin, and is, therefore, under the control of the thyroid mechanism, naturally the effects of the latter mechanism and thyroid extract are far more effectual and successful than any other glandular extract. If, however, the hypophysial mechanism is primarily involved, the effects would be seen in the tissues under its control, while primary thyroid disease would not alone be manifested in the ectodermal tissues, but if the disease persisted for any length of time, the tissues under hypophysial mechanism control would likewise give rise to symptoms and changes.

Theoretically, hypothyroidism means hypoproteinism, and vice versa hyperthyroidism means hyperproteinism as assumed that the thyroid secretion controls the rate of deamination. Furthermore, a decrease or increase of parathyroid and suprarenal medulla secretions will through their action produce hypo- and hyperproteinism respectively.

That in myxedema there is present hypoproteinism and in exophthalmic goiter hyperproteinism are familiar facts to all. The close relationship of the thyroid, parathyroid and protein metabolism is also shown by the following extracts taken from McHarrison's(100) experiments, "Approximately, thirty-three per cent of the offspring of goitrous parents are born with normal thyroid and parathyroid glands. Where there is congenital disease of the parathyroid glands there is also congenital disease of the thyroid gland. Congenital parathyroid disease is due to the action on the fetal gland of toxic products of anaerobic organisms absorbed from the maternal intestines. Congenital goiter is due to the action on the fetal thyroid of toxic substances derived from the intestine." He also drew attention to the previously undescribed nervous symptoms from which about one-third of all cretins suffer, and attributed the condition, which he named nervous cretinism, to parathyroid defect. He concluded by stating that the defect in cretinism is one of the whole thyroid mechanism of the parathyroids as well as the thyroid gland.

Tetany, like goiter, occurs in endemic and epidemic form. It may follow infections, and Oddo suggests that it may only be active in the presence of some special form of perverted digestion. The similarity between infectious diseases and exophthalmic goiter is being noted regularly. Sabourin(101) calls attention to the frequency of symptoms suggesting exophthalmic goiter in the course of tuberculosis. He calls this special form "petit Basedowisme." And again, "Biolokur(102) (in the Russky Vrach, Petrograd) thinks that there is a causal connection between tuberculosis and Basedow's disease. In ten per cent of his tuberculous patients he found symptoms of exophthalmic goiter; predominantly in women, one man to ten women. Symptoms of excessive thyroid functioning may occur in the very incipient stage of tuberculosis. They seem independent of the gravity of the case, the age, sex, etc. In fact, he thinks that symptoms of Basedow's disease may indicate the existence of a latent tuberculous infection. When tuberculosis symptoms are pronounced the symptoms of Basedow's disease change the clinical picture, producing a thyroid-tuberculosis combination. Successful treatment of the exophthalmic goiter symptoms may improve the pulmonary process." The latter statement, according to the present hypothesis, should read, "Successful treatment of the pulmonary process may improve the exophthalmic goiter symptoms." In tuberculosis, a chronic protein disturbance is set up by the tubercle bacillus, and as it gives off its toxic protein, the thyroid mechanism must increase its function, thus resulting in the suggestive symptoms. The longer an infection persists the more apt are the suggestive symptoms to make their appearance. Pottenger(103), in analyzing the symptoms of tuberculosis, classifies them according to toxic, reflex and those due to the tubercular involvment itself.

Scattered through literature are reports of cases of acute enlargement of the thyroid gland being almost without exception an accompaniment of infectious diseases. Strümpell(104) says, "There can be no doubt that every time food is taken in large amount, there is a temporary increase in the activity of the heart, the frequency of the pulse and the tension. This is in part because the specific gravity of the blood is temporarily increased by the material taken into it and in part because the products of metabolism in the blood have a direct stimulating action upon the heart or blood vessels, finally because the excessive ingestion of liquids temporarily increases the total amount of blood." In the second part of this statement is seen a possible connection between a temporary stimulating condition and a permanent one, as seen in exophthalmic goiter.

That there is an increase in protein products in the blood following a hearty meal seems to be proven by the experiments of Tranter and Rowe(105), who observed through the refractometric method the determination of albumin, globulin and nonprotein in normal blood-serum. In their one case, the total amount of albumin was proportionately increased one hour after a hearty meal. Furthermore, the total albumin was very much higher than any one in their series, the normal average being 6.20 per cent, while in this case it was 7.79 per cent with a globulin per cent of .66, average in series 1.74. While of course not conclusive, nevertheless it is suggestive.

Since there appears to be an increased protein content in the blood after a hearty meal, the thyroid mechanism would increase its function, and so the clinical evidence tends to show. Chas. Beeson(106) says that out of three hundred and sixteen cases of pellagra, thyroid disease complicated twenty-five, more than twice as many as the other complicating diseases. Morse(107) found in this disease degenerative changes in the thyroid and suprarenals.

It is interesting to note the adrenalin content of the suprarenals under certain pathological conditions. The changes noted in the suprarenals following infectious diseases has long been known and have been studied experimentally. Roux and Yersin(109) described a high-grade hyperæmia in guinea-pigs following diphtheria infection or intoxication. Charrin and Langlois(110) found a marked hyperæmia and increased volume in the suprarenals following picrotoxic injections and Pettit(111) was able to show the histological changes. Marked changes in the suprarenals, namely, necrosis and hemorrhages, were found by Bogomolez (112) after infection with diphtheria bacilli; Tarchanow(113) after Bacillus pestis; Labzine(114) after streptococcus. These hyperæmic suprarenals following infection contain, according to Langlois, the active blood-pressure raising substance in almost limitless quantities. While in chronic infections with the suprarenals enlarged three to four times their normal volume, this substance is almost lacking.

The suprarenals obtained from rabbits dying of diphtheria toxemia and various other bacterial toxins do not, according to

Luksch(115), contain the blood-pressure raising and mydriatic substance. This author has found that suprarenal extract taken from animals poisoned with phosphorus or with uremia was inert, while that taken following hunger and fever and alkali poisoning as well as severing of the spinal cord was potent. Schur and Wiesel(116) found, after double nephrectomy, epinephrin in the blood and changes in the chromaffin tissue network, this being evidenced by chromaffin cell masses in the suprarenal medulla as well as chromaffin cell masses. Following long standing kidney irritation and damage, it is possible to produce hypertrophy of the suprarenal medulla as well as that of the free chromaffin bodies. Molnar and Goldzieher(117) found in rabbits epinephrin in the blood following subcutaneous injections of boiled kidney juice and the histological examination of thirty cases of chronic nephritis in humans revealed hypertrophy of the suprarenals.

Since the hypophysis is an ectodermal structure, and having shown that to some extent conditions of the thyroid are often reflected in the hypophysis, the latter mechanism will now be considered. It was found after careful study that this mechanism has under its control the cells derived from the mesoderm. The hypophysial mechanism consists of the following:—

1. The anterior lobe of the hypophysis (analogous to thyroid).
2. The posterior lobe of the hypophysis (analogous to parathyroids).
3. The suprarenal cortex (analogous to the suprarenal medulla).
4. The cells of mesodermal origin.
5. Carbohydrate and fat metabolism.

The function of the anterior lobe is similar to that of the thyroid gland and, like it, is the keystone of this mechanism. It is the activator of carbohydrate and fat metabolism, the amount of its secretion will determine the rate of carbohydrate and fat metabolism in the blood. This portion of the gland is essential to life, as proven by Cushing(118) and confirmed by the experiments of Biedl(119) and others. The posterior lobe, which is not essential to life, according to experiments, and the suprarenal cortex, like the parathyroids and suprarenal medulla, have a two-fold action, namely, they are amboceptors or building stones which act on the carbohydrate and fat products in the blood, and likewise sensitize the cells of mesodermal origin. The action only takes place when the posterior lobe or suprarenal cortex secretion has sensitized the mesodermal cell and has united with the carbohydrate and fat metabolic products in the blood. It will be seen that whenever the hypophysial mechanism is diseased, the mesodermal cells are the ones which show the pathology and symptomatology.

The deduction that the anterior lobe of the hypophysis through its secretion activates carbohydrate and fat metabolism has been made from clinical and experimental studies. Delille(120), by giving injections of hypophysial extracts over a course of fourteen months, found a decided increase in the fat assimiliation of four rabbits. The close relationship of carbohydrate and fat metabolism is well known, and it is to be recalled that Beta and oxybutyric acid formation are common in diabetics. In disturbances of the hypophysial mechanism, it would be expected that any part of the mechanism would bring with it disturbances of carbohydrate and fat metabolism. What would be a striking support to the theory advanccd is the statement of Falta that the *pancreatic insular apparatus* is mesodermal in origin. Thus can be seen how the anterior lobe may influence the carbohydrate metabolism. This point cannot be elaborated upon at present, since all authors are not agreed that the apparatus is of mesodermal origin. It would, however, readily fit in with the theory and go far towards explaining carbohydrate metabolism and many other more obscure points.

The tissues derived form the mesoderm are as follows:

I. Mesenchyma.
    (a) Connective tissue.
        1. Cutis.
        2. Tendons, etc.
        3. Cartilage.
        4. Bone.
        5. Marrow.
    (b) Lymph glands.
    (c) Spleen.
    (d) Blood-vessels.
        1. Blood (in part).
    (e) Lymphatic system.
    (f) Fat Cells.
    (g) Smooth Muscle.

II. Mesamœboids.
    (a) Leucocytes.
    (b) Red blood cells (embryonic).
    (c) Marrow cells.

III. Mesothelium.
- (a) Peritoneum.
- (b) Pleuræ.
- (c) Urogenitals.
    - 1. Wolffian body.
    - 2. Kidney.
    - 3. Ovary.
    - 4. Oviduct.
        - (1) Uterus.
        - (2) Vagina.
- (d) Striated Muscles. (Cardiac cell muscle.)

Theoretically, then, these are the tissues that must show the pathology and give the symptomatology in diseases of the hypophysis. Naturally, the posterior lobe and suprarenal cortex sensitize different parts of the mesoderm. From the evidence, it has been deducted that the posterior lobe sensitizes the cells derived from the mesenchyma and amœboids, while the suprarenal cortex (whose origin is from the mesoderm), sensitizes the cells derived from the mesothelium.

Since protein disturbances are much more common because of the bacterial diseases, disturbances of the hypophysis are not as common as those of the thyroid. However, a prolonged thyroid mechanism disturbance is certain to produce, in the course of time, changes in the hypophysis. In connection with these remarks may be mentioned Salamous'(121) discussion of harmless diabetes in the young. He says that one of the features of the case was familial character, and that the patients had a neuropathic character, and that after excitement the proportion of sugar in the urine was higher, regardless of diet. The most likely cause of this is, no doubt, to be ascribed to thyroid mechanism disturbance with resulting change in the hypophysis. This will be discussed with adrenalin glycosuria.

Acromegaly, being the typical disease of the hypophysis, it shall be used as an example to demonstrate the hypophysial control of the mesodermal cells.

Connective tissue, cartilage, bone, etc.—The subcutaneous tissue is thickened by connective tissue growing in and around the fat lobules, sometimes forming fibrous tumors. Similar growths surround the sweat glands and nerves, and sometimes pass between the nerve fibers. (Note the following in contrast to thyroid diseases): The hair follicles, sweat glands, and blood-vessels in the skin are not notably altered. The connective tissue overgrowth also occurs in the muscles. This connective tissue alteration is present in many parts of the body. The nose, tongue, hands, etc., all have an increase in connective tissue. The larynx becomes enlarged, so that the voice of both men and women becomes a deep pitch. All the bones of the body are more or less strikingly enlarged. The bones of the extremities show very marked enlargement. The cranial skull becomes much enlarged and the ribs thicker. This bony enlargement is a true hyperplasia.

Lymph-glands.—The lymph-glands are enlarged. The following extracts from Falta(122) show the changes in the *blood-vessels:* "The vascular system in the later stages of acromegaly almost always show changes. A slight grade of arteriosclerosis develops. Microscopical examination shows that the three vascular coats are involved in these changes, and that the media becomes poor in muscle fibers. Varices are striking frequent." Hemorrhoids are also of frequent occurrence. *Blood (in part).* Mononucleosis and hypereosinophilia is the rule in acromegaly.

Fat cells.—An increase in the deposition of the fat cells is everywhere apparent.

Smooth muscle.—The intestines in acromegaly may be double their length. (Musculature increase?)

Mesothelial structures.—Peritoneum and Pleuræ.—No mention of these latter structures is made in postmortem reports, so that no evidence can be presented concerning changes in these parts. Theoretically, however, an increase in the thickness of these layers would be expected in the beginning of the disease.

Kidneys.—The kidneys are strikingly large, and on microscopical examination show enormously large glomeruli.

Ovary, Testicle.—Falta(123) says: "Here we mostly find premature lessening or loss of function.—At beginning of the disease there is found, not at all rarely, signs of increased function." After the disease has persisted for some length of time, the ovaries and testicles are found to be degenerated and oogenesis and spermatogenesis are absent. Why these conditions are present will be fully discussed with the sexual glands and their relation.

Urogenitals, Uterus, Vagina.—The external genitalia often show a distinct hyperplasia. The penis, the labia manora, and the clitoris may increase in dimensions. This persists to the end of the disease. The vagina also increases in length. The uterus is invariably small.

Striated Muscles.—"In many cases the muscle strength is not diminished in the initial stages. Sometimes such individuals show even extraordinary strength."(123) Muscular weakness generally follows later in the disease. The heart often hypertrophies to an enormous degree, sometimes known as the "cor bovis." It soon degenerates, however.

The hypophysis in these cases is generally adenomatous. There is an increase of the glandular structure and therefore an increase in the function of the hypophysial mechanism. Theoretically, the suprarenal cortex should share in this hyperfunctioning, and such is the clinical and pathological finding. The suprarenal cortex is almost invariably hypertrophied. Falta(124) is again quoted: "In two cases Fischer found enormous suprarenals; the enlargement affected especially the cortex; also Delille saw this several times. Lately Fischer and Schultz found enlargement of the suprarenals in two cases of acromegaly, in one of which (a case of early acromegaly) the suprarenals were enlarged about five times at least." The abnormal hairiness, so often present in both men and women in this disease, will also be discussed with the sexual glands.

In the early stages of acromegaly, there is a lessened tolerance for carbohydrates and frequent glycosuria, while in hypoactivity there is an increased tolerance and no glycosuria. This would lend support to the view taken in regard to the hypophysis and carbohydrate metabolism control.

The anterior lobe, being essential to life, is similar in many respects to the thyroid. It is the keystone of the mechanism. Cushing(125) showed that the anterior lobe is essential to life, while partial removal resulted in disturbances of growth, carbohydrate and fat metabolism, and in sexual gland changes. In the early stages of acromegaly, there is found in about forty per cent of cases, glycosuria and in the later stages, when hypoactivity sets in, an increased tolerance for carbohydrates. Clinically, it is seen that in cases of acromegaly, the thyroid gland is enlarged and this enlargement is due to a true hyperplasia of the glandular tissue. The hypothesis would be in accord with such findings.

The action of the posterior lobe is a sensitizing one on the mesenchymal cells. The marked physiological action of its extract would tend to prove this. It causes contractions of the smooth muscles. The blood pressure is raised through its action on the blood vessels. It has been shown that its action is directly on the muscle cells and independent of sympathetic nerve innervation. The action on the carbohydrates as assumed in this article is also supported by the physiological action. Goetsch, Cushing and Jacobson(125) found a decreased tolerance for carbohydrates following its injection. This was more marked in animals whose tolerance had been raised by previous extirpation of this lobe. As the discussion of the hypophysial mechanism proceeds, it will be seen that the action of the posterior lobe is exclusively on the mesenchymal cells.

The action of the suprarenal cortex on carbohydrate and fat metabolism is borne out by certain facts. Forchheimer(126) says, "Recently attention has been called to certain changes in carbohydrate metabolism in this disease (Addison's), which afford further proof of a relation of the suprarenal glands to carbohydrate metabolism. Experiments on animals deprived of their suprarenals have revealed interesting relations of these glands to carbohydrate metabolism. Bierry and Malloisel(127) and Porges(128) have found a condition of hypoglycemia. Porges found the same in three cases of Addison's disease." The hypoglycemia is probably due to both loss of suprarenal medulla and cortical secretion, and besides its other actions, the action of the medullary secretion on the posterior lobe is lessened and the cortical secretion on the carbohydrate products is also lessened.

In the suprarenal cortex are found the cortical cells with the lipoid nuclei, called cortical nuclei. The nuclei are intensively stained by the fat-staining dyes (Sudan III, Scarlet Red). A. C. Croftan(129) has found in the *cortical* substance a *diastatic ferment.* There is also found in the cortical portion a considerable amount of *cholia.* Guerrini(130) and F. Marino-Zucco(131) in 1888 showed that watery extracts of the suprarenals contained cholin, called at that time, neurin. Cholin is a split product of lecithin. The lecithins are saponified by alkalies, yielding fatty acids, the glycero-phosphoric acid and cholin. Like the true fats, they are soluble in ether. According to Biedl(132) cholin is a product of the cortex.

The suprarenals also contain lipoids, and the fatty content of these glands was demonstrated long ago. These lipoids, as has abundantly been proven, belong to the cortex, which, as remarked before, contain the lipoid granules. Acccording to Kölliker(133) there are certain animals whose cortex assumes a yellowish-white color. Forchheimer(134) says, "The most characteristic function of the cortex is its content of doubly refracting lipoid substances; among these, lecithin and certain esters of cholestrin are especially abundant. Hunt isolated cholin from the suprarenals; later Lohmann showed that about nine times as much of this substance could be obtained from the cortex as from the medulla. The hypothesis has been suggested that one of the functions of the suprarenal cortex is to make and secrete lipoids for use in other parts of the body." Biedl(135) gives the percentage of lipoids in the dry substance of the suprarenals as sixty-two per cent. He says that this wealth of lipoid substance in the cortical portion makes it possible that its function is to supply the body with necessary fat-building substances. In Biedl's work may be found abundant references to the lipoid and carbohydrate action of the suprarenal cortex. Hypoglycemia has been reported by Bierry and Malloisel(127) in suprarenalectomized animals. Eppinger, Falta and Rudinger(136) found that phloridzin produced only a slight glycosuria in suprarenalectomized dogs. Furthermore, they found a high carbohydrate tolerance in Addison's disease.

There is a host of evidence to prove that the suprarenal cortex secretion controls the cells of mesothelial origin. Loss of the suprarenals or hypertrophy of the cortex should theoretically result in atrophy and hyperplasia respectively of these tissues, and so it is found clinically. First, its action will be considered when hypofunctioning or its secretion is entirely absent. "Novak(137) studied this question (action on sexual organs) on one hundred and sixty-six rats, finding that the genital organs in young rats showed extreme changes after the adrenals on both sides had been removed and the sexual functioning was correspondingly much reduced. The atrophy and hypoplasia of the genital organs were more pronounced the younger the rat at the time the adrenals were removed."

In anencephalous individuals, there is found, as previously mentioned, aplasia of the suprarenals. In these fetuses are also found under-development and anomalies of the genital organs. In the hypothesis, it was assumed, therefore, that the anecephaly and suprarenal medulla are related, while the suprarenal cortex and genital organs are related as stated. Since there is a plasia of both medulla and cortex, the theory is in harmony with the fact that there is lack of brain and genital development. Cases are often reported in which the secondary sexual characteristics do not develop, and accompanying this is a degenerative or sclerotic changes in the suprarenal cortex. In Addison's disease, it was seen that among other symptoms there is a marked asthenia in the striated muscles, including the cardiac muscle, and amenorrhea and impotency in the male. The muscles which have no sympathetic innervation are the striated muscles, and these are derived from the mesothelium.

Biedl(138) has concluded from extirpation experiments on animals in whom the two parts of the glands are separated, that it is the loss of the cortical substance which causes the asthenia. Hoskins(139) of this country also comes to the conclusion that it is the loss of cortical substance which causes the asthenia. Concerning the amenorrhea and impotency, Kyrle(140) has found a deficient spermatogenesis and degenerative changes in the interstitial glands in Addison's disease. Congenital hypoplasia of the suprarenals invariably results in marked degenerative changes in the testicles. The kidneys in Addison's disease are also altered—they are smaller than normal. Pigmentations of the peritoneum have been found by some authors, which Osler(141) says is not considered of importance. This is mentioned merely to show that these cells (mesothelial) are also altered.

In hyperfunctioning of the cortical portion, the tissues derived from the mesothelium share in the hyperfunctioning. Forchheimer says, "An association between tumors of the suprarenals and precocious sexuality has been found; the fact that this condition occurred with tumors of cortical and not with those of the medullary origin suggests that the former part has some relation to the sex organs. On the other hand, it is stated that in Addison's disease and in congenital hypoplasia of the suprarenals, there are marked changes in the testicles." Hyperplasia is especially noted in the cortex in cases of hemaphroditism.

Falta,(142) in discussing adenomata of the cortex, says, "They may proceed from the cortex itself, or may originate in the separated germs of the cortical system in the kidney or in the genitalia, etc." Furthermore, he goes on to say that "with the development of such hyperfunctionating cortical tumors in the childish organism, there occurs an enormously accelerated development of the body, a premature development of the genitalia." There are hundreds of cases reported in which hyperplastic conditions of the cortex resulted in sexual changes. Quite frequently, also, are reported cases of women who shave, are masculine in character, with deep pitched voices, etc., have hyperplastic conditions of the cortex. In these individuals are associated an overdevelopment of the musculature. It will be remembered that in acromegaly there is usually a suprarenal cortex hyperplasia. The kidneys are strikingly large in this disease. Falta(143) says in part in describing acromegaly that there is "marked accentuation of the function of the genital glands after preliminary transitory increase of function and apparently, frequently hyperplasia of the suprarenal cortex." It will be seen, therefore, that there is an increased function present and theoretically due to the cortex. Why this is not a lasting condition will be discussed with the sexual organs and their function.

Furthermore, as remarked by Kaufmann,(144) in hypoplastic conditions of the suprarenals, besides the brain defects, there are defects in the urogenital system. The case of Launois, Pinard and Gallais(145) is interesting in this regard. A nineteen-year-old girl menstruated at the age of thirteen. At seventeen, violent vomiting, gradually colossal obesity, mental changes, cessation of menstruation, emaciation, then diffuse depilation, and only then hypertrichosis and myasthenia. The girl appeared to be much older than she was. She had a black beard and mustache. At postmortem were found a tumor of the right suprarenal. This illustrates the muscular asthenia and underdevelopment of the ovaries. In this brief review of symptomatology and pathology of the suprarenal cortex it is seen that cortical hyploplasia results in failure of development of the mesothelial tissues.

In hyperplasia of the suprarenal cortex, attention is called to the fact that there is a hyperdevelopment or hyperfunctioning of the mesothelial tissues. In that type of tumors known as the hyperfunctionating cortical tumors or hypernephromata, there is seen in the child before puberty an enormous development of the genitalia and internal sexual organs. This results in precocious sexuality, with its characteristic development of body and mind. In other words, the secondary sexual characteristics appear very early. There is no doubt that the premature development of the sex glands accelerates body growth through its stimulating action on the other ductless glands. How this is accomplished will be discussed later.

There are many cases reported of suprarenal cortical tumors with an accompanying precocious sexual development. Bullock, Sequeria,(146) Glynn(147) and others gave early reports of these findings. In cases of pseudo-hermaphroditism, hyperplastic conditions of the suprarenal cortex are invariably present. Marchand(148) first reported the autopsy findings. He found colossal hypertrophy of the suprarenal cortex and a large accessory suprarenal. Such hyperplastic conditions are to be expected in the cortex when these mesothelial structures are increased in number and character. Interesting is the fact that hypernephromata at the menopause give rise only to obesity. Since the ovaries have been developed and their function is now in abeyance, no marked changes in the other tissues are to be expected. The hairiness found in these cases will also be considered later.

Hyperplastic changes are found in the suprarenal cortex during rut or in pregnancy (Guieyesse,(149) Stoerk,(150) and V. Haberer.(151) Falta(152) says, "When the cortical tumors develop in the fully developed organs, the manifestations are quite different. Here there comes about a pronounced disturbance of the functions of the sexual glands with involution of the uterus, and in addition a tendency to obesity and to the development of hairiness, both of which with respect to abundance and localization are entirely masculine. The influence of the suprarenal cortex on the hairiness is especially unmistakable in all the conditions mentioned. We find abnormal hairiness in pseudohermaphroditism feminus, in the premature development in childhood, in the cortical tumors that develop in the adult organism; perhaps just in cases of acromegaly with hyperplasia of the cortex, and finally, as is known, in pregnancy, in which hair begins to grow in places that otherwise represent the virile type. Therefore, it seems necessary that in the future, when the question is asked as to which influences the secondary sexual characters have to thank for their origin, attention should be paid to the suprarenal cortex. The near relationship that the suprarenal cortex and the substances of the sexual glands show embryologically and morphologically seems also to exist in the function of these parts."

It was said in the hypothesis that the hair development is controlled by the parathyroids, and in the next chapter on the sexual glands, it will be shown that the suprarenal cortex produces these changes only secondarily. Rolleston(153) and Molon(154) have called attention to the resemblance of the cortical cells to the luteal cells. In acromegaly, as has been noted, the kidneys are frequently of a very large size and there is present a true hyperplasia as shown by microscopic section. Enormously enlarged glomeruli are seen. In two cases, Fischer(155) found immense suprarenals; the enlargement affected especially the cortex; also Delille(156) saw this several times. Lately, Fischer and Schultze(157) found enlargement of the suprarenals in two cases of acromegaly, in one of which (a case of early acromegaly) the suprarenals were enlarged five times at least. Kidney changes are therefore quite uniform.

It is also evident that the musculature in pseudo-hermaphroditism becomes quite masculine, as the striated muscles are derived from the mesothelium. Schur and Wiesel(158) saw in partially nephrectomized animals a hyperplasia of the suprarenals. This is possibly a compensatory measure on the part of nature.

The hypophysial mechanism has under its control many important structures, and it greatly influences thereby the body development. Since the hypophysial mechanism is controlled by the thyroid mechanism, it can be understood why the osseous and genital systems in cretins are under-developed. It is because of the lack of stimulating thyroid secretion on the hypophysis. On the other hand, feeding thyroid extract to the very young increases bony growth. It is used by some of the profession to stimulate callous formations in fractures. For the same reason, the changes in carbohydrate as well as in protein metabolism can be understood. As the thyroid is the keystone of the thyroid mechanism, so is the anterior lobe of the hypophysis the keystone of the hypophysial mechanism. If there is hypofunctioning of the anterior lobe, then there is hypofunctioning of the posterior lobe and suprarenal cortex, and the same is true of hyperfunctioning. The mesodermal structures share in these processes. This holds good in all functioning diseases of the hypophysis.

Hyperfunctioning of the hypophysis means also hypercarbohydratism and increased fat metabolism, while hypofunctioning results in a hypocarbohydratism and increased tolerance plus a sluggish fat metabolism. The statement made by Van Noorden(159) that the glycosuria in acromegaly shows a striking independence from the sugar value of the diet, is easily understood. In the early stages of acromegaly there is a hyperfunctioning of the hypophysis and a lessened carbohydrate tolerance, while in the later stages a heightened tolerance is present. It is also to be remembered that diabetic disturbances of metabolism occur in Basedow's disease, the so-called thyreogenic glycosuria. According to the theory, the cause lies in the stimulating action of the thyroid on the hypophysis. Falta comes to the conclusion that the anterior lobe of the hypophysis involves in some way carbohydrate metabolism, not by mobilizing the carbohydrates in the liver, but by an increase of the combustion in the periphery. The hypothesis is in accord with this conclusion.

Salamous'(121) article in regard to harmless diabetes in the young was previously mentioned. In these cases, a familiar characteristic and nervous temperament was noted. After excitement, the proportion of sugar in the urine was higher irregardless of diet. The close connection to the thyroid is very apparent here. The diabetes is due, according to the hypothesis, to the action of the suprarenal medulla on the posterior lobe of the hypophysis.

Since the parathyroids sensitize the anterior lobe of the hypophysis, disturbances in carbohydrate metabolism should be present when the former are diseased. When, as in tetany, the parathyroid secretion is diminished or absent, then there should result a disturbed carbohydrate metabolism. Falta(160) says, "in parathyroidectomized dogs, the assimilation limits for dextroses are regularly reduced. Falkenburg and R. Hirsch, and also Frank P. Underhill and Tadasu Laiki, found this after parathyroidectomy and referred it to the absence of the thyroid gland." This is regarded in this hypothesis as directly due to the parathyroid absence. According to the experiments of Eppinger, Falta, and Rudinger,(161) the glycosuria following thyro-parathyroidectomy is due to the absence of the parathyroids.

On the assumption that the bone development is under the control of the hypophisial mechanism and more particularly of the posterior lobe, it would not be unreasonable to suppose that calcium metabolism, which is so intimately connected with bone formation, is also under hypophysial control. Von Moraczewski(162) found in a case of acromegaly pronounced retention of phosphorus, calcium, magnesium, and chlorin, and also nitrogen, and explains this by the increased growth of tissue. Through feeding hypophysis tablets, the calcium, magnesium, and phosphorus excretion were increased. Very little has been done in regard to experimental work on salt metabolism in acromegaly and it is only on clinical grounds that it can be assumed that the hypophysis is connected with salt metabolism. As is well known, calcium metabolism is very materially affected in tetany. According to MacCallum and Vogtlin,(163) the calcium contents of the brain of parathyroidectomized dogs was lowered as was that of the blood.

The fact that the healing of fractures is delayed and callus formation slowed, as determined by Morel(164) and Canal,(165) is not very surprising. This is due to the lack of sensitizing action of the parathyroid on the anterior lobe which, as has been said, is the pacemaker of the hypophysial mechanism. Erdheim(67) showed that callus formation in parathyroidectomized dogs is poor in calcium, while Leopold and V. Reuss(166) found the skeletons of parathyroidectomized rats poorer in calcium than the control animals. Quite convincing are the findings of Schüller,(167) who found in chronic tetany a characteristic rarefaction of trabeculæ and marked atrophy in the bones as shown by the x-ray. These findings are also confirmed by Falta,(168) who remarks, however, that such findings as these were also found in cases which had no tetany. Attention is also called to the fact that in diabetes as well as in tetany a frequent formation of cataract is often present. The ciliary epithelium and lens of the eye are, as the reader will recall, of ectodermal origin and sensitized by the parathyroids, so that it may be assumed that in certain forms of diabetes there is a disturbance of both the parathyroids and hypophysis. Kahn and Falta(169) observed Chvostek's sign in cases of severe diabetes; it is also found, however, in other severe metabolic disturbances. What would also seem to be confirmatory evidence of a sensitizing action of the parathyroids on the anterior lobe of the hypophysis is the fact that in tetany there are very marked disturbances in growth, delayed ossification, and atrophy of the bones, so that this again brings to mind the small stature of the cretins with the failure of the thyroid mechanism. The combination of tetany and osteomalacia will be discussed later.

Those interesting and important ductless glands, the sexual glands, will now be discussed. In this article, only the internal secretion portion of these glands will be considered. The many problems that these glands are involved in are so numerous that only a very few points can be touched upon. The problems of psychology, body, mind and character development have a most important relation to these glands. Their importance on body and mind development is readily seen following castration in the young.

One of the many disputed points that has arisen in discussing the sexual glands is whether the so-called "soma cells" possess a sex of their own or whether the sex is determined by internal secretory factors. The latter view is upheld in this article. Another much disputed question is what determines the sex of an impregnated ovum. Some writers take the view that all the cells of the embryo are sexually differentiated, and, on the other hand, others claim that this is only determined secondarily. The latter view is also adhered to in this paper.

Before discussing the questions above, the relations between the sexual and other ductless glands will be given. The sexual glands can be divided into two parts—the interstitial glands, which consist of Leydig's cells, and the glands of generation, which in man are the seminiferous tubules and Sertoli's cells, and in women the follicular apparatus. In giving the functions of these sexual glands it has been assumed that through their secretion they are *antagonistic* in action to the posterior lobe of the hypophysis, the parathyroids and suprarenal medulla. In other words, these exert an inhibitory action on one another. It produces an increased secretion from the thyroid and hypophysial mechanism. Since the suprarenal cortex sensitizes the sexual glands and since it is part of the hypophysial mechanism, it can be seen that when the latter mechanism is functioning very actively, it will call forth, through the action of the suprarenal cortex, an increased sexual secretion, and thus Nature tries to maintain an equilibrium. However, a persistent hyperactivity of the hypophysial mechanism will, in time, lead to atrophy or degenerative changes in the sexual organs. This will receive consideration later.

At the time of puberty, all the ductless glands are called upon to their fullest extent in order to stimulate growth and development of the body cells. This is manifested by thyroid, hypophysial, suprarenal, and sexual glandular development. The increased thyroid and hypophysial secretions bring about a growth in the tissues normally under their control. When the sexual glands are fully developed and capable of forming spermatozoa and ova, the girl and boy approach man and womanhood. At this time the nervous system is sensitive to all impressions and self-analysis becomes one of the characteristics. As for the nervous disturbances, these become very apparent, especially in the young lady.

It is a well-known fact that the female is more subject to disturbances of her sexual glands than is the male, since she has the problem of menstruation to deal with. Each month, a ripe follicle bursts with the consequent formation of an ovum, and this is followed by the corpus luteum, to which is attributed, in this article, the antagonizing secretion. As this cycle is normally gone through each month, it is obvious that the relative amount of thyroid and hypophysial secretions in the female are greater than in the male. The equilibrium maintained between the latter secretions and the antagonizing corpus luteum secretion is relatively greater. Quite naturally, therefore, her nervous system is more subject to disturbances. Because of this peculiar equilibrium maintained between the ductless glands, as stated, and the female sexual glands, her brain is smaller than that of the male; she is more sensitive, shy, modest, and subject to disturbances of her gray matter, such as hysteria, neurasthenia, psychoses, and to exophthalmic goiter. Note also the fine texture of woman's skin and the distribution of the hair and its finer quality. A lessened ovarian secretion should theoretically result in a masculine type of woman.

There is a host of evidence to show this antagonistic action. First will be considered the antagonistic action between the suprarenal medulla and the ovaries and testicles. If the tissues sensitized by the suprarenal medulla are again brought to mind, the number of disturbances that lack of its sensitization produces is overwhelming. Since all the higher centers of the brain are in the gray matter, psychological disturbances are to be looked for in suprarenal disease. Naturally, character development also comes under its scope. It is, of course, well-nigh impossible to consider all the disturbances this can create. For obvious reasons, puberty is the time when nervous disturbances are apt to make their appearance. If the individual inherits any "nervous predisposition" from either parent, the ductless gland activity at this time is likely to bring forth the occult predisposition. As an example, dementia precox, in which, it is very interesting to note, there is a thyroid enlargement in perhaps a majority of cases. This enlargement has been noted by a great many neurologists. Feeding thyroid extract to these individuals gives beneficial results, but they are not brilliant. Perhaps if the feeding of thyroid extract had begun in infancy the results might be more striking. The thyroid enlargement is no doubt a compensatory measure.

Notice at the time of puberty the shyness and modesty of the average girl. Her vasomotor system (sympathetic) is irritable and easily upset, as evidenced by blushing. The impressions made on the nervous system at this time generally last throughout active life. They remain more or less latent, but evidence themselves frequently in the characterization of an individual. It is not surprising, as assumed that the suprarenal medulla secretion controls the optic thalamus, the emotional center, that many nervous disturbances originate in fright or great emotional strain. The most striking example is exophthalmic goiter, the origin of which is ascribed by many to sympathetic nervous system disease.

It would hardly be permissible to overlook, in relation to this discussion, the Freudian theory of sexual life. While, perhaps as in all other branches of medicine, the enthusiasm of the individual carries him too far, nevertheless a conservative viewpoint must grant that the foundation for Freudian teaching and theory is a sound one. The present hypothesis is in accord with the Freudian teachings. As assumed by Freud, hysteria is the result of ungratified sexual desires. Applying the present hypothesis to the problem, it would mean that ungratified impulses from the sexual glands call forth an increased suprarenal medulla secretion, stimulating the gray matter of the nervous system. The constant stimulus from the sexual glands to the suprarenal medulla and therefore to the higher centers of the brain results in an accumulation of nerve impulses, which in time results in a nervous explosion or discharge known as the globus major of hysteria. Again it is obvious from physiologic reasons why the female is more liable to this affection. Evidently the ancient teaching that the cause lay in the uterus (from which the word takes its origin, ("uster")) is not so far amiss. The many bizarre types of psychic changes also find a ready explanation. The male is, as stated, less subject (one to ten) to hysteria than the female as his impulses, while stored up in the optic thalamus and higher centers, have an exit in the so-called nocturnal emissions.

So in pregnancy, the change in mentality that is so frequently seen is due to the lessened suprarenal medulla secretion because of the more active sexual glandular secretion. It thus inhibits the action on the gray matter with the resulting mental changes. This is not always marked, as the thyroid and pituitary mechanisms through hypertrophy overcome this. This does not of course mean that these mechanisms simply hypertrophy to overcome sexual glandular activity, but to stimulate metabolism. Naturally, there are various degrees of disturbances between these glands at this time. That the sexual glandular secretion is very active during pregnancy is shown by the fact that the corpus luteum is persistent for four months and there is, as proven by autopsies, an enormous increase in the interstitial glands as well as a suprarenal cortex hyperplasia. Chloasma, or the pigmentation of pregnancy, is also explained by the hypothesis. In these women, the active interstitial or sexual glandular secretion gives rise to a lessening of the suprarenal medulla function with the resulting pigmentation as previously explained.

It has been noted quite recently that vomiting of pregnancy is frequently relieved by corpus luteum feedings. This no doubt holds the suprarenal medulla's action on the vomiting center in check. Recall the vomiting in Addison's and Basedow's disease. And for similar reasons corpus luteum extract is beneficial for nervousness following the menopause or even before this, as at the menstrual periods.

The psychological problems that this hypothesis brings to mind are very many and in particular those relating to sexual psychology, a subject upon which many volumes have been written. It is not within the scope of this article to review or apply the principles to these various problems, but it can be readily understood if the principle outlined is grasped. An active sexual glandular secretion—and by this is meant the internal secretion part of the gland—calls forth an increased amount of suprarenal medulla secretion. The sexual impulses are stored in the psychic centers as kinetic energy, which when an excess has been stored become kinetic. In the insane, and particularly those who have inherited their insanity, there are brain defects and the pscyche is not well developed. A manly character is therefore lacking. Since true brain defects are often accompanied by suprarenal atrophy, it is not surprising that sexual perversion in these individuals is very frequent. Their sexual organs are usually normal or over-developed and are functionating freely, thus inhibiting the suprarenal medulla secretion.

Eunuchs have no testicular secretion, with the result that the suprarenal medulla secretion is also lessened, as the equilibrium has been offset by testicular removal. A eunuch is generally apathetic, lazy, lacks character, and suffers from lassitude. The will power, ambition, "backbone," and "spunk" of normal men are missing. On the other hand, sexual excesses may also do harm, for the constant exaggeration of stimuli resulting in a hyperfunctioning of the suprarenal medulla finally gives rise to an exhaustion of the latter with the consequent nervous disorders.

The antagonistic action between the posterior lobe of the hypophysis and the sexual glands will now be considered. It will be recalled that there is an enlargement of the hypophysis, a marked accentuation of the interstitial glands, followed later by a loss of function and very frequently hyperplasia of the suprarenal cortex, in acromegaly. There is, at first, an increase in the function of the hypophysial mechanism with its hypophysial enlargement and hyperplasia of the suprarenal cortex, the latter increasing the function of the interstitial glands, as they are of mesothelial origin. Acromegalic individuals have at the beginning of the disease an increase of libido, and frequently in women an increased menstrual flow. But as this hypophysial secretion is a persistent one, it gradually overcomes that of the interstitial glands with the resulting atrophy and loss of function of the latter. Now the parathyroids, the suprarenal medulla and posterior lobe rule with a free hand and there is a temporary increase of function. Very characteristic is the abnormal amount of hairiness seen in acromegalics; this is considered as due directly to the increased parathyroid function and only indirectly to the suprarenal cortex. It must be understood that at the beginning of acromegaly, the increase in interstitial gland function produces an increase of the posterior lobe, parathyroid and suprarenal medulla secretion to maintain the equilibrium. This is manifested by abnormal hairiness, the occurrence of outbreaks of sweat, psychical excitement, epinephrin glycosuria, and of course the increase in mesenchymal tissues, which are sensitized by the posterior lobe. As the disease persists, the antagonizing action of the interstitial glands is gradually being overcome so that atrophy and loss of function is seen in the latter glands. The parathyroids, suprarenal and posterior lobe functions decrease so that finally there is noted pigmentation, muscular asthenia, etc. Since the suprarenal cortex is hyperplastic, the fact that the external genitalia are increased in dimensions is not at all surprising. A hypertrophy of the thyroid gland in acromegaly is also a condition easily understood. Delille(156) and Renon showed that following repeated injections of hypophysial extract there was a hyperplasia of the suprarenals.

In hypophysial dystrophy there is found depositions of fat, an inhibition of development of the genitalia and secondary sexual characteristics such as hairiness, voice changes, etc. The pathology is found in the glandular hypophysis. Since the hypophysis is primarily affected, the whole hypophysial mechanism function is interfered with. The suprarenal cortex, therefore, also shares in the hypofunctioning as part of this mechanism. The mesothelial structures, the ovaries, testicles, uterus, prostate, etc., therefore, do not develop, and because of this the secondary sexual characteristics do not appear. Men have no beards, and the voice does not change. Menstruation and ovulation fail to appear. Frequently, the testicles fail to descend. Falling out of the hair (parathyroid function) is not uncommon. There is, in contradistinction to the early stages of acromegaly, an abnormally high carbohydrate tolerance. During youthful years, if the disease appears then, there is an inhibition of growth and ossification. This is due to the hypophysial dysfunctioning.

The hypophysis controls the only pronounced instance of embryonic development remaining in adult life, namely, oogenesis and spermatogenesis.(170) Rupture of the Graafian follicle is brought about by disappearance of the blood-vessels and lymphatics and a fatty degeneration of the cells of the membrana granulosa and discus proligerus. On reaching maturity the follicle bursts, discharging its contents containing, besides the liquor folliculi, the ovum. Following this, the corpus luteum is formed. The mesenchymal structures, such as the fat, blood-vessels, blood (in part), lymphatics, etc., are under posterior lobe control and during menstruation there is a degeneration of these structures in the ovarian follicles and uterine endometrium. Theoretically, then, its (posterior lobe) function must be inhibited. During the premenstrual period the thyroid and hypophysial mechanism are active, as the thyroid and hypophysial enlargements tend to show. The hypophysis has been shown to be enlarged during menstruation. Seven to nine days before menstruation the blood pressure is raised and falls again with the beginning of the flow. The glycosuric action of adrenalin is increased. There is also recorded an increase in the polymorphoneuthrophiles, all this pointing towards posterior lobe hyperfunctioning. The suprarenal cortex increases in size in the premenstrual and before rut periods of animals. There is likewise noted an increase in the reflex excitability and an increase in the mental alertness. Falta(171) thinks many of these manifestations point to an increased function of the chromaffin tissue. Halban(172) believes that there is an increased growth of any beard that may be present. This is ascribed to parathyroid increase.

While the thyroid and hypophysial mechanisms are increasing their function at this time, the suprarenal cortex being part of the latter mechanism, increases its function (as demonstrated) and sensitizes the interstitial glands with greater vigor. However, as has been assumed, the latter glands are antagonistic to these mechanisms, and the sensitizing action of the posterior lobe (as well as the parathyroids and suprarenal medulla) is held in check. Its action on the blood vessels, lymphatics, etc., is interfered with, resulting in degenerative changes in the follicle. Such changes also take place in the uterus. With the bursting of the follicle comes the ovum, followed by the corpus luteum, containing the antagonistic substance. If the hypothesis is correct, then certain clinical changes in the tissues sensitized by these mechanisms will become manifest at this time. Note the pigmentation of the areolae, "circles" under the eyes, and acne menstrualis, occasional changes in mentality, as proof of this antagonistic action. When the corpus luteum disappears, the thyroid and hypophysial mechanisms again go through the same cycle. Ovulation and menstruation can, according to this, be independent of one another. Fraenkel(173) has taken the view that the retrogression of the corpus luteum gives rise to menstruation.

It may be safely assumed that in the ninth month of pregnancy, and more particularly during labor, that the posterior lobe secretion is becoming the more active. This is clinically manifested during labor by uterine contractions, which are due, it is thought, to the action of posterior lobe and suprarenal medulla. The addition of the fetal hypophysial and suprarenal medulla secretion is undoubtedly a factor in bringing on labor. McCord's experiments seem to support this. "Physiologic reactions characteristic of extracts of pituitary and suprarenal glands were obtained by McCord from bovine fetal glands during all developmental stages in which the microscopic recognition of the glands is possible. For the pituitary gland, this period is from the eighth week to full term. The presence of the active principles of these glands at so early a developmental period suggests that the fetus in utero may be under the influence of its own internal secreting glands as well as the maternal glands."(174)

It would seem very probable that when the amount of suprarenal medulla and posterior lobe secretions were in excess, *i.e.*, at the end of pregnancy, then contractions of the uterus begin and expulsion of the fetus and placenta results. The physiologic action of posterior lobe extract during labor is well known, as is the action of the suprarenal medulla secretion on the sympathetic fibers of the uterus.

During the ninth month of pregnancy and during labor a hyperleucocytosis is present. Baer,(175) in his summary, says there is a leucocytosis of pregnancy appearing in the ninth month, slight in amount and especially noticeable in primiparae. The leucocytosis of labor is marked in primiparae, averaging 18,250, and is increased by a duration of labor beyond twenty-four hours. This is mentioned because in this hypothesis the posterior lobe has been assumed as controlling the bone marrow, lymph glands, spleen and blood in part. Its secretion, as mentioned previously, is very active during the ninth month and especially during labor.

As further evidence that such is the case, may be mentioned the fact that amenorrhea is usually present during lactation. Since the hypophysial mechanism is the controlling one during labor and puerperium, it would seem that carbohydrate and fat metabolism are increased during these periods. In support of this view is the fact that milk is secreted which contains seven per cent sugar and four per cent fat. The process of involution is one of fatty degeneration, absorption, and atrophy. If the hypothesis were correct, *i.e.*, posterior lobe secretion in excess, then it can be understood how this fatty degeneration and atrophy takes place. The corpus luteum secretion is absent and held in check by the posterior lobe secretion. The following is also interesting and has the same explanation: "It is known that in connection with involution the uterus becomes smaller at one period than even the nonparous organ, and that it undergoes regeneration either during or after the lactation period. If the uterus is studied microscopically during this period, the muscular fibers are seen to have undergone atrophy, while the usual fatty changes of involution are also in evidence. The part played by the ovaries in this connection is not known."—Edgar.(176)

As syphilis is a frequent cause of abortion, it may be interesting to see how expulsion of the fetus is produced. The *spirochoeta pallida* (*treponema pallida*) produces toxins. This causes an activation of the thyroid mechanism. It has been noted that the syphilitic toxin destroys the ovum, and naturally the antagonizing corpus luteum secretion is lost, and thus the suprarenal medulla and posterior lobe secretions are the controlling factors, resulting in uterine contractions. The secretion of milk comes in following either a nine months' pregnancy or an abortion; this has been observed as early as the second month of pregnancy.

The following extracts from Falta(177) tend to support the above remarks: "The extirpation of the ovaries, other than during pregnancy, may increase the existing secretion of milk, while, as is known, the occurrence of menstruation (ovaries active) during lactation inhibits the secretion of milk and indeed in the premenstrual period, and also that amount of its solid constituents, especially the casein, the fat and the salts are diminished (N. Davis). Halban, therefore, concludes that the ovary is growth-inducing and secretion-inhibitory on the mammary glands, just as is the placenta, only less so." Surgeons are aware that too much handling of the adnexa while operating will result in an abortion or miscarriage during pregnancy. This destroys the corpus luteum. The blood of the newborn shows a leucocytosis, and in some even a secretion of colostrum is present as well as signs of epithelial proliferation.

At the climacteric, the interstitial glands atrophy and theoretically an increase in the tissues sensitized by the thyroid and hypophysial mechanisms should take place. Acromegalic features, hair growth, and a masculine habitus are often seen. The voice may become deeper in pitch. Adiposity of the women at the climacteric is very common. Psychical irritability, hot flashes, etc., are part of the symptoms. Psychoses of different types are prone to make their appearance. The fact that many of these symptoms (hot flashes, etc.) are relieved by corpus luteum extract favors this antagonistic view.

It may not be amiss at the present to say that it is when the sexual gland function is diminished or absent (climacteric) that tumors are prone to make their appearance, for the antagonistic secretion is then lost. If, of course, it can be proven that the thyroid and hypophysial mechanisms control the cells, as stated in this hypothesis, then it would be reasonable to suppose that they are in some way connected with the abnormal growths of these cells. However, the tumor and ductless gland problem will be left for a later discussion.

The combination of tetany and osteomalacia is a very frequent one, and this tends to lend support to the hypothesis and likewise the antagonistic action between the interstitial glands and the posterior lobe. Since osteomalacia occurs almost exclusively in women and in the overwhelming majority of cases during pregnancy, the hypothesis would seem to be especially applicable here. The ovaries have been regarded as being responsible in some way for osteomalacia. It is generally conceded that the ovaries are too active in this disease. If such is the case, then the interstitial gland secretion inhibits the action of the parathyroid's, posterior lobe and suprarenal medulla's secretions to too great an extent. The action, then, of the parathyroids on the anterior lobe is lessened and the action of the posterior lobe on the mesenchymal cells is also lessened, resulting in the softened bone. The combination of tetany and osteomalacia should then be not at all infrequent. Note also that *pregnancy and menstruation* are predisposing causes for both osteomalacia and tetany. Furthermore, castration leads very often to a rapid and complete cure or at least to an amelioration of the symptoms. Möbius(178) reports a case of Basedow's disease that later developed myxedema and then had puerperal osteomalacia. (Thyroid and hypophysial mechanism exhaustion?)

As further proof of the inhibitory and antagonistic action of the corpus luteum on the glands mentioned, it is noted that the glycosuric action of adrenalin and also its action on the heart and blood vessels is lessened. Pituitrin has exerted a favorable influence on osteomalacia. Pal observed that extracts of the anterior lobe influenced osteomalacia favorably.

Menstruation, as mentioned, is found to be a predisposing cause for tetany. Krabbe(179) reports a case in which tetany occurred during menstruation, and this was relieved by implantation of parathyroids into the tibia. This has been questioned by some writers, however. It was previously mentioned that the parathyroids control hair development. Falta(180) ascribes hair development to the suprarenal cortex, a point with which this hypothesis does not agree, as the cortex only involves hair development secondarily through its control of the sexual glands, which are antagonistic and as said, stimulating thereby, to the other ductless glands. Puberty is the ideal time for such a study.

Sabourand,(181) who has studied for twenty years the pathology of the scalp, believes that falling of the hair and its growth are linked with physiologic genital development. He says that children, women and eunuchs never become bald like men. Certain affections of the scalp, developing exclusively in children, such as tinea tonsurans, always subside at puberty. The adult scalp seems invulnerable to this form of tinea. Furthermore, he says, "Aristole asked centuries ago why men alone become bald."

Theoretically, the answer to the latter would be as follows: "Man has not the problem of menstruation to deal with, and has not, therefore, the same equilibrium between the testicular secretion and the parathyroids, suprarenal medulla and posterior lobe, as a woman. She has the corpus luteum, the antagonizing secretion to deal with each month, and in turn, therefore, this calls forth an increased amount of parathyroid, suprarenal medulla and posterior lobe secretions. In other words, the relative amount of her secretions is much greater than that in a man. It is, however, the parathyroid which controls the hair development. Children do not become bald because the testicles and ovaries have not developed, therefore the antagonistic secretion on the glands as mentioned is not present. For the same reason eunuchs do not become bald, for the parathyroids have no antagonizing secretion to deal with and sensitize the skin and its appendages unhindered.

It will be recalled that in acromegaly there is an extensive hair development. Not alone in normal places does the hair become thick, but in abnormal situations. Hair on the trunk and extremities becomes very dense. The transitory increase of interstitial gland function followed later by an atrophy is, as will be recalled, part of the disease. The temporary increase calls forth more parathyroid, suprarenal medulla, and posterior lobe secretions. Since the interstitial glands atrophy, the latter for a time, at least, sensitize their structures (as the hair), unhindered, resulting in the symptoms previously described.

Alterations in function of the thyroid gland and goiter are frequent occurrences. Slight hyperthyroidism in acromegaly is a common feature. Magnus-Levy(182) and Salomon(183) have recorded several cases and called special attention to this. This would again tend to show that an increased thyroid mechanism function results in an increased hypophysial mechanism function, as the hypophysis is under thyroid control, being of ectodermal origin. Theoretically, if this hyperthyroidosis should continue, then the hypophysial mechanism increase should also continue. This statement is borne out, for in the later stages of acromegaly (hypophysis not active), myxedematous symptoms appear very frequently. Glycosuria is, as stated previously, common in acromegaly. Case reports of this are numerous (see Falta). Improvement of myxedema symptoms are produced by thyroid feeding and uninfluenced by hypophysis feeding.

The difference in the equilibrium maintained between the sexual glands and other ductless glands in the female and male is present from birth, as clinically shown by the fact that girls walk and talk earlier than boys. A girl reaches womanhood sooner than a boy does manhood. Experimental work also proves this difference. Falta(184) says, "According to this we would expect that when the sexual glands are extirpated in a not yet fully developed animal and the sexual glands of the opposite sex are implanted in this animal, the original predisposition would come to development even then. Steinach has followed this method. He implanted ovaries into previously castrated young males of guinea-pigs and rats. The transplants 'took,' and not only the interstitial glands developed, but also the primary follicles with normal ova, and there occurred in entirely normal manner the formation of atretic follicles of corpora lutea. In these animals not only did the penis cease developing, but it was even set back in its development. If a tube and a piece of the uterus were transplanted with the ovary, these developed to mature organs. Moreover, there came about an enormous development of the mammary glands, that in form and size were entirely like those of normal females, and indeed even exceeded them in size. Furthermore, the animals remained behind in growth; the body showed proportioning of the female; also the growth of hairs and the layer of fat showed the texture of that of females. And there was a reversal of the psychical characters."

It may be concluded if these experiments of Steinach's are correct, that the sexual equilibrium in the male is changed through the transplanted ovarian tissue, thus strengthening the hypothesis advanced. As Chérau,(185) a French physician, said, "Propter ovarium solum mulier est quod est," and as Virchow(186) said, "Das Weib ist eben Weib durch seine Generationsdrüse. Alle Eigentümlichkeiten seines Körpers und Geistes—kurz alles, was wir an den wahren Weibe, Weibliches bewundern und verehren, is nur eine Dependenz des Eierstockes." According to the hypothesis, the determining sex factor would lie in the relation of the corpus luteum or interstitial cells of the testicles and the suprarenal medulla, parathyroid and posterior lobe secretions. The latter, in turn, sensitize their respective tissues. In other words, the equilibrium maintained between the ductless glands is the determining factor. The results of menopause, acromegaly and castration show that these women have a tendency to masculinity. On the other hand, eunuchs and males with deficient testicular secretion have certain feminine characteristics. Such changes are apt to be more pronounced the earlier this deficient or absent testicular secretion manifests itself.

What determines that a fetus will be a male or female or possess some of the elements of both is to be considered in relation to the hypothesis. As previously stated, the experiments of McCord have shown that the active principles of suprarenal and pituitary secretions are present in the fetus and that the fetus in utero may be under the influence of its own secreting glands as well as the maternal glands. The sex would be determined by the amount of sexual glandular secretion in the fetus derived from the maternal glands. Perhaps the thyroid and hypophysial mechanism secretions of the fetus plus the maternal gland secretions swing the balance one way or the other. The amount of thyroid and hypophysial mechanism secretions of the fetus plus the maternal gland secretions, if in large amounts, would result in a female, while the lesser secretions would produce a male. In another way, it may be said that if the thyroid and hypophysial mechanism secretions, which are antagonistic to the corpus luteum, are lessened in the fetus, a male will be produced, whereas the greater activity of these secretions in the fetus results in a female.

Cases of true hermaphroditism are not known in man, but cases simulating both sexes are not at all uncommon, that is, hermaphroditus spurius. In these individuals, either one or the other sex predominates. If cases of true hermaphroditism did exist in man, that is, that every male and female element was present and functionating, then the hypothesis advanced would not answer. But it has been assumed in these cases of hermaphroditism spurius, that the antagonizing sexual secretion and thyroid and hypophysial mechanism secretion balance has been upset some time in intrauterine life, that is, if the secretions were of greater amount and intensity, the female element was predominating and the female character was developing, and later this is upset so that it is lessened throughout the rest of intrauterine life and this gives rise to the male organs and character. That this is probable is shown by embryological facts in man, for the Mullerian tract leaves remnants in its cranial and caudal ends, in what are known as rest forms of Hydatide and as the uterus masculinus. It can be deducted therefrom that every fetus is potentially bisexual, and the sex is determined by the interrelationship of the ductless glands. The different varieties, combinations and degrees of pseudohermaphroditism are determined by the amount of secretions and the length of time they are predominating. In summary it may be said that the sex is determined by the amount of thyroid and hypophysial mechanism function and its relation to that of the ductless gland secretions of the mother.

There still remains to be discussed in relation to the present work, the function of the thymus gland. It is generally conceded that this gland is concerned with the formation of blood cells. Its action is supposed to be present only during early life. Some observers claim it is active only during intrauterine life; the majority, however, come to the conclusion that its activity is seen until the time of puberty. Hammar has found that the average weight of the gland at birth to be 13.26 gms., and that the weight increases up to puberty, averaging 37.52 gms. between the ages of eleven and fifteen. It gradually diminishes from that age on.

The gland is composed of two lateral lobes. Each lateral lobe is composed of numerous lobules held together by delicate areolar tissue, the entire gland being enclosed in an investing capsule of similar but denser structure. The primary lobules are made up of small follicles which are irregular in shape and are more or less fused together, especially toward the interior of the gland. Each follicle consists of a medullary and cortical portion, which differ in many essential particulars from each other. The cortical portion is mainly composed of lymphoid cells supported by a delicate reticulum. The medullary portion contains few lymphoid cells, but there are especially toward the center granular cells and concentric corpuscles.

From a study of the subject, it has been concluded that the cortical portion is concerned with a hematopoietic function, while the medullary portion has an antagonistic and inhibitory action on the thyroid and hypophysial mechanisms. Through its action on the suprarenal cortex, it holds the development of the sexual organs in check.

The antagonistic function of the thymus will first be considered. If the thymus is removed very early in life, naturally its antagonistic action is lost and at this time the thyroid, hypophysial and sexual systems do not respond as in later life, that is, there is no exciting stimulus in infancy as at puberty and later. On this account the function of the thyroid and hypophysial mechanisms is lessened instead of increased, as it is found when the testicles or ovaries are removed in later life. The results of thymectomy, as found by experimenters, is not very uniform. Among the symptoms resulting from this, are a delayed growth, ossification of bones is retarded, while callus formation following fractures is delayed, the skin becomes soft and pasty, there is a marked increase in the peripheral nervous excitability (Chvostek's sign in tetany), muscular tremors are present, there is loss of weight, cachexia, a diminished intelligence, indolency and idiocy. Basch,(187) Hart, Nordmann,(188) Klose and Vogt(189) seem to have found these findings as constant.

If the hypothesis be correct, then there should be noted changes of a hyperplastic nature in the sexual glands, for the thymus is antagonistic to the suprarenal cortex, which is a link in the hypophysial chain. Paton(190) found that thymectomy caused a rapid growth of the testicle, while involution of the thymus occurred especially early in breeding animals. Since the thymus is absent, there results an increase of the suprarenal cortex function, as evidenced by hypertrophied testicles and ovaries (Bartel(191) and Hermann.(192) Quite naturally, then, the thyroid and hypophysial mechanisms should also increase their function. It must be remembered, however, that the sexual glands have reached their maturity before the natural time, and this on the other hand results in a too mature production of active secretion which is antagonistic to the parathyroids, suprarenal medulla, and posterior lobe secretions, thus holding the action of the latter glands in check. The cells sensitized by these various secretions show this inhibitory action, such as, for example, the increased excitability of the peripheral nervous system (Basch), delayed dentition, diminished intelligence, idiocy, indolency, soft, pasty skin, and the lack of ossification. On the other hand, the fact that involution of the thymus occurred rapidly in animals used for breeding purposes is to be ascribed to the fact that here the active corpus luteum in these older animals calls forth the secretions from the parathyroids, suprarenal medulla, and posterior lobe.

The embryology of the thymus has been more or less in doubt, but quite recently, through studies on this problem, Hammar,(193) Maximow(194) and their followers have come to the conclusion that it is an epithelial organ with a proliferation of lymphocytes derived from the mesenchyme. The latter make up the greater part of the thymus. His(195) and Stieda(196) adhere to the assumption that there is a secondary ingrowth of mesodermal pictures. This would make it belong to the lymphatic apparatus. Falta(198) believes it to be of endodermal origin. He says there is a "symbiosis of cells of the different germinal layers." The reticulum is the epithelial structure and assists in forming the so-called Hassal's corpuscles. Pappenheimer(199) in a recent article says that "morphologically the small thymus cells are identical with lymphocytes to the last detail. Their complete independence of the epithelial constituents of the gland has been demonstrated in tissue cultures by the writer and by Wassen." Furthermore, he says that he has been able to prepare a cytotoxic serum by immunizing rabbits with thymus lymphocytes, and this serum both agglutinates and cytolizes suspensions of lymphocytes. "On the whole, therefore, we may regard it as assured that the thymus is a *lympho-epithelial* organ in which the two types of structures co-exist in the most intimate relation."

From such a study, then, it may be assumed, as stated in the hypothesis, that the medullary portion is probably of epithelial origin, while the cortical portion is derived from the mesenchyme. Hammar(193) has also shown that the thymus grows progressively until sexual maturity is reached. As to whether the thymus is essential to life is still open to question; some (Klose, Vogt,(189) Flesch and others) hold that it is, while on the other hand, others (Nordmann,(188) Pappenheimer(199)) think that it is not. Be that as it may, there is no question that it is related to the ductless gland system and has a reciprocal relation. The thymus is related to the sexual organs, as abundantly proven by various experiments.

If the thymus is of lympho-epithelial origin, as has been claimed, then it would be affected in diseases of the thyroid and hypophysis, for the epithelial structures are under the control of the thyroid, while the blood-forming system is controlled by the hypophysis (posterior lobe). This is apparent around the age of puberty, for before this time in infancy particularly, the medullary portion (regarded as being of epithelial origin) is antagonistic to these mechanisms. Enlargement of the thymus should be not uncommon, then, in diseases of the thyroid and hypophysis. Its frequent enlargement in exophthalmic goiter is well known. It is also seen in acromegaly. The results of thymus dysfunctioning are to be looked for before or during the period of puberty. Since it is established that the thymus is related to the sexual development, then at puberty, as stated, pathological conditions due to hyperactivity will become manifest. A few experiments will suffice to show that the thymus is related to sexual development. Soli(200) found following thymectomy a deficient or absent spermatogenesis in the testicles of rabbits and guinea-pigs. Klose and Vogt(201) found a transient hypertrophy of the testicles followed by atrophy. Here, of course, the reciprocal relation between the thyroid and hypophysis has been destroyed and in this instance the hypophysial mechanism (suprarenal cortex) increases its function. But the relation is destroyed, resulting in a lessened activity with a resulting atrophy of the testicles. Hewer(202) found that irradation of the thymus caused a degeneration in the testicles. Fulci(203) found that pregnancy accelerated involution of the thymus, while Bomprani(204) noted that lactation inhibited regeneration of the thymus. It will be recalled that the thyroid and hypophysial mechanisms are the controlling secretions during lactation.

As previously stated, diverse results are reported concerning the effects of thymectomy. It seems established, however, that an effect is constantly seen on the sex glands. Henderson(205) reported that early castration caused a further of the thymus and a prolonged or delayed involution. Paton(206) claims that thymectomy in sexually immature animals leads to a rapid growth of the testicle. The hypotheses advanced would be in accord with these findings, for as stated the medullary portion of the thymus is antagonistic to the hypophysial mechanism (suprarenal cortex), which controls sex development. Since the sex glands, while inhibitory to the thyroid and hypophysial mechanisms, through their action call forth secretions from the latter mechanisms, then it can be understood why castration prolongs and delays involution and in fact results in thymus hyperplasia. And on the other hand, thymectomy results in a rapid growth of the testicle in sexually immature animals because the antagonistic influence of the thymus is lost, resulting in a hyperplasia of the testicle. Theoretically, this would be followed by atrophy, especially in very young animals, as the stimulating antagonistic secretion is lacking. The best results would apparently be found in very young animals.

Speaking for the mesodermal origin of at least a portion of the thymus is the fact that in some fishes the thymus is the only organ producing lymphocytes. If such is the case, that the cortical portion of the thymus is of mesodermal origin, then the haematopoietic organs are the bone marrow cells, the spleen, the lymphatic apparatus, and the cortical portion of the thymus. According to Hammar (Keibel and Ball(207)), "the thymus is from the beginning a paired organ and it remains so permanently; neither fusion of the two anlagen by transverse connections nor a complete division into several lobes occurs." In Keibel and Ball's "Embryology," the statement is made that "authors are agreed only as to the epithelial origin of cellular reticulum and of Hassall corpuscles. The chief elements of the organ, however, the small thymus cells, have been regarded either as immigrate cells and therefore as thymus lymphocytes (more recently especially by Maximow and Hammar) or as modified epithelial elements (among recent authors chiefly by Stohr).(208)

In reviewing the subject on the embryology of the thymus, the summary of the majority of the authors, then, is that this organ is of lympho-epithelial origin. A hyperplasia of the thymus would not be an infrequent condition in hyperfunctioning of the thyroid and hypophysis. In the latter conditions, mononucleosis should also be the rule, and so it is found. The lymphocytosis of exophthalmic goiter is very well known. In acromegaly, Sabrozes and Bounes,(209) Messedaglia,(210) Rath,(211) Exner,(212) and many others have found lymphocytosis. Since the cortical portion of the thymus is part of the haematopoietic apparatus, the lymphocytosis of infants is easily understood. What would seem to be further evidence in favor of an antagonistic action between the thymus and thyroid mechanism is the statement of Falta(213) to the effect that the thyroid is essential for the development of the hematopoietic process and that in infantile myxedema the involution of the lymphatic apparatus is deficient.

It seems likely from an embryological and clinical study that the cortical portion of mesenchymal origin works in conjunction with the hematopoietic apparatus, namely, the lymphatic glands, spleen, bone marrow, while the medullary portion with its reticulum is antagonistic to the thyroid and hypophysial mechanisms. Clinical studies, then, should either support or disprove the tenabilty of such a theory. Take for instance thymico-lymphaticus. In this disease, the individual possesses a weak constitution; the lymphatic glands, such as the tonsils, the lymphatics of the tongue, intestines, stomach and spleen, are all hyperplastic. The bone marrow is very red, and the thymus is very much enlarged. Accompanying this there is a hypoplastic aorta and heart, and peripheral blood vessels, a colloid degeneration of the thyroid, and a delicate bone structure. To this must be added a hypoplastic condition of the genitals, a narrow vagina, an infantile uterus, anomalies of menstruation in the female, and an infantile type of genitals in the male. Theoretically, the cortical portion of the thymus stimulates the hematopoietic apparatus, while the medullary portion holds the thyroid and hypophysial mechanisms in check. In this disease, as reported by Wiesel and Hedinger,(213) there is regularly found a slight development of the chromaffin tissue. Since the posterior lobe is also held in check, then the heart, aorta and peripheral blood vessels are under-developed, as are the bones. Here would seem to be a contradictory statement, for the lymphatics are of mesenchymal origin, and therefore the lymphatics and spleen should be hypoplastic. However, it would seem that only the hematopoietic portion of the mesenchyme is hyperplastic while the rest is hypoplastic. Judging from the study of the subject, it is assumed that the cortical portion of the thymus and hematopoietic portions of the mesenchymal tissues are in a direct relationship, and the hematopoietic portion of the mesenchyme reflects the condition of cortical portion of the thymus. Mononucleosis should be the rule in these cases. Explainable also is the mononucleosis of the eunuchoid individuals. Here the under-developed sex glands are not functionating properly, permitting a persistency of the thymus.

In favor of an antagonistic action betewen thymus and thyroid and hypophysial mechanisms are the following facts: In thymectomized young dogs there is seen a marked change in the osseous system. The bones about two to three weeks following the extirpation are softer and more pliable than the control animals. The gait is unsteady. The hind extremities are weak and thin. The animals are indisposed and are inclined to rest on their hind legs more so than the control animals. Later the fore extremities become curved, and the whole growth is retarded. The psyche and intelligence is diminished, and the sexual glands are small. Basch(187) proved the osseous changes by fracturing the hind legs of thymectomized and control animals living under the same conditions. In order to break the operated dog's legs, less force was necessary than used in the control animals. Very early (five to seven days) the difference of callus formation appeared. The operated dogs had very much less callus than the control animals. This was still present several weeks following. Röntgen rays also proved this to be the case. The difference was more marked in younger animals. When thymus rests were still present in some of the animals, the differences noted were less marked. Furthermore, Sommer and Floerken(214) reported that there is roughening of the coats in thymectomized animals. Basch(215) has shown that thymectomy in young dogs results in galvanic irritability in the peripheral nervous system. This irritability of the peripheral nervous system was much less when thyro-parathyroidectomy was also performed on these animals. Injections of calcium salts into the cerebral cortex of thymectomized animals lessens the peripheral irritability, according to Sabatani.(216) Basch(187) thinks tetany of infants is due not alone to the parathyroids, but to all the bronchiogenic organs. Biedl(217) says, however, that many of the suckling animals have parathyroid bodies in the thymus and ascribes the tetany to their extirpation.

Thymectomy, then, theoretically results first in an increase of the thyroid and hypophysial mechanism and later in a decrease of their secretions with the clinical manifestations of bone cartilage, sex glands, blood, hair, peripheral nervous excitability, psychic changes, and chromaffin system hypoplasia. Clinical evidence should afford proof of such a theory. Rachitis frequently precedes and accompanies lymphatism, as does tetany (hyperplastic thymus).

Since chlorosis almost always makes its appearance at the time of puberty or during the maturation time of the female organism, it is necessary to say a few words in regard to this disease. Diseases in the genital sphere are found almost constantly. At this time of the female development, all the ductless glands are functionating actively. It seems quite reasonable to assume that some of the ductless glands are not equal to the task or that the sexual glands are too active, thus inhibiting the thyroid and hypophysial mechanism action. Morowitz(218) believes that the disease is due to a disturbance in the reciprocal action of the ductless glandular system. According to Tandler,(219) V. Noorden(220) and others, there is found in some families simultaneous occurrence of chlorosis and prepubital eunuchoidism. Hastings Gilford(221) reports a case of childish gigantism with sexual prematurity and chlorosis. This case was observed between the second and eighteenth years. The child's menstruation began at the age of thirteen months and was irregular until the eighth year. At the thriteenth month a rapid growth of the whole body took place, and at three and one-half years her development as shown by x-ray plates of hand corresponding to that of an eight-year-old girl, while the sexual development of that of a thirteen to fourteen-year-old child. From the sixth to the twelfth year she was treated for chlorosis. Her intelligence remained somewhat behind. According to the hypothesis, the thymus gland would be in a hypoplastic state, thus permitting the thyroid and hypophysial mechanism to develop too early. That the hypophysial mechanism is functionating prematurely is shown by the excessive bone development, and since the suprarenal cortex is a link in this mechanism, the mesothelial structures would mature too early, as seen by the premature sexual development. This premature sexual development leads to an early antagonistic action of the ovarian internal secretion on the suprarenal medulla, posterior hypophysis and parathyroids, thus inhibiting their action after a time. The lowered intelligence (medulla) and the presence of chlorosis speak for such an action. Falta(222) assumes an exhaustion of the ductless glands through premature sexual development. All in favor of an antagonistic action ón the thyroid and hypophysial mechanisms would be the hypoplastic conditions of the arteries, the poikilocytosis, the high carbohydrate tolerance, the relatively small heart, the hypoplastic condition of the chromaffin system, the low blood pressure, pigmentations of the skin, psychic changes, the small uterus, the small external genitalia. A hyperplastic thymus would explain the production of these symptoms. Virchow(223) said there was a *congenital* arrest in the development of the aorta and larger arteries as indicated by their small size, their soft and elastic walls in chlorotics. He ascribed the disease as due to the non-development of the vascular system. Unfortunately, there are but few post mortems on chlorotics, so that the condition of the thymus is not definitely known. The blood, in part, the vascular system, the bone marrow, lymphatics and spleen, are all mesenchymal in origin, and blood changes should occur. It is further to be mentioned that the heart muscle is softened. The hypoplasia of the arteries and genitals is congenital, thus speaking in favor of an early inhibitory action. There is also noticed in chlorosis a certain muscular weakness which cannot be explained alone by the poor blood condition, as people with a higher and severer grade of anemia do not show as much muscular weakness in proportion. Myasthenia gravis has been ascribed as due to a persistent thymus. Psychic changes such as craving for innutritious articles of food, such as seen in pregnant women, is also present. Constipation is the rule. In reviewing the pathological and clinical evidence, it is believed that the disease chlorosis is due to a persistent hyperplastic thymus and the manifestations of it become apparent at the age of puberty when the ductless glands are called upon for their secretions.

In regard to infantilism, it is believed in this hypothesis as being due to a persistent thymus with the resulting antagonistic action on the thyroid and hypophysial mechanisms. This applies to the cases of true infantilism as defined by Falta.(224) He defines "a pure infantilism as a standing still at the infantile stages of development, considering especially the following factors: the genitalia and the vita sexualis remain undeveloped, or develop deficiently; and the same is true of the secondary sexual characters, the *involution of the lymphatic apparatus is deficient,* the growth is deficient, ossification that is, the appearance of bone nuclei and the closure of the epiphyses is delayed, and the childish dimensions of the body are retained wholly or in part; that is, the lower length of the body equals the upper length or, what is commoner, exceeds it only a little; the form of the pelvis is neither (of the) masculine nor feminine (type), but infantile, and finally the psyche remains behind (in development). Such individuals show throughout no gross defect in intelligence, but their minds remain childish."

Important then is to distinguish between cretinism and infantilism. In the former there are degenerative changes and defective development, while in the latter there are no degenerative changes but a standstill development. As stated in the definition, the involution of the lymphatic apparatus is deficient. It is to be emphasized then, according to this hypothesis, that the persistent thymus results in maintaining a permanent antagonistic equilibrium between the thyroid, hypophysial mechanisms and its own secretion. In other words, the thymus secretion keeps the development of the cells under the thyroid and hypophysial mechanism control in the infantile stage. The equilibrium is of the infantile type. It does not check the secretions of these mechanisms entirely, but maintains the infantile equilibrium past the normal period. Naturally the sexual glands are not going to develop. We have therefore a co-ordinated inhibition of development. Since the thymus is persistent in these cases, infantilism and tetany should not be rare and so it is found clinically. It may be stated, then, that the functioning of the ductless glands in infantilism is of the "child type." Combinations of the hypofunctioning type of ductless glandular disease should not be at all uncommon in this disease, for example, the above mentioned infantilism and tetany, infantilism and rachitis, infantilism and progressive muscular dystrophy (hypophysial mechanism), infantilism and hypoplastic vascular system, infantilism and dystrophea adiposo-genitalis, childish psyche, etc. According to this hypothesis, in summary may be said that the persistent thymus continually produces a secretion after its normal time of involution, which maintains the infantile equilibrium between the thyroid and hypophysial mechanisms, thus preventing their respective cells from maturing as in the normal adult.

In contrast to infantilism is the disease, gigantism. There is a distinction between gigantism and acromegaly, but it is a matter of degree only. Both diseases are due to hypophysial changes. An attempt will be made to explain the degree of difference. If the hypophysis is affected before the development of the sexual glands, then there results gigantism. If, however, the hypophysis is affected (hyperplasia) after the sexual glands have *fully* developed, then acromegaly results. This is understandable because the hyperplasia of the hypophysis is not being held in check by the sexual glandular secretion, thus permitting the hypophysial mechanism to sensitize the tissues undisturbed. The sexual glands evidently are being held in check by the excessive hypophysial secretion, so that the suprarenal cortex's action on the sex glands (as part of this mechanism) is offset by the former excessive action. Acromegaly always develops later, after the sex glands have matured and the bones have become more or less thoroughly ossified and therefore the height is proportionately lower. The degree of gigantism depends entirely upon when the hypophysis was affected, the earlier, the more pronounced the gigantism, and vice versa. Massalongo(225) designates acromegaly as late gigantism, and Brissaud(226) and Meige(227) believe that acromegaly and gigantism are the same disease and due to the same cause. The hypothesis would agree with these statements, and as before said, the relative sizes of the individuals and bone changes are due to the time of sexual development. The sex glands then are of especial importance in this disease as well as the hypophysis.

There remains to be mentioned in this article, the pineal gland. Reports concerning this gland are somewhat meager and conflicting and it would therefore be mere speculation as to its function. It has been deemed best, therefore, not to draw any definite conclusions concerning this gland. From reports (Ogle,(228) V. Frankl-Hochwart,(229) McCord(230) and others), it would seem that the gland is, perhaps, related to sexual development and body growth. The gland seems to be active until about the seventh year. Marburg(231) is of the opinion that hypopinealism produces premature development of the genitalia; hyperpinealism produces universal obesity and apinealism to cachexia. Marburg has, according to Falta, given up the idea that hyperpinealism produces obesity. Quite recently, according to some authors, the feedings and injections of pineal gland substance and extract produce absolutely no results. It is to be noted that in some cases (Raymond and Claude)(232) there is found a hyperplasia of the suprarenal cortex. This would account for the sexual changes. Jordan(233) states that he could find no histological evidence of a glandular function of the pineal body. He believes that the pineal gland in sheep functionates actively only during the first eight months of post natal life. Important to mention is the fact that the hypophysis is so often encroached upon and may also account for some of the trophic changes noticed, such as adiposity, sex changes, premature hair development, etc. (hypophysial mechanism). Pineal gland tumors, it is to be noted, also result in dystrophia-adiposo-genitalis. So, in summary, it may be said that the function of the pineal gland is more or less speculative.

As for the pancreas, only the insular apparatus of this gland was mentioned in this article, and that in connection with the anterior lobe of the hypophysis. If of mesodermal origin, then it can be readily understood how the anterior lobe, through hyperfunction, will stimulate this insular apparatus of the pancreas, and vice versa, hypofunctioning will cause a decrease in its function. However, as before stated, no further elaboration of this important point will at present be attempted until further proof is securėd as to the embryonic origin of the insular apparatus. Let the reader bear this in mind. (Hansemann(197) claims the apparatus to be of mesenchymal origin.)

SUMMARY

1. The thyroid mechanism, consisting of the thyroid gland, the parathyroids, and suprarenal medulla, control the cell development of the ectodermal tissues.

2. The thyroid gland is the keystone to this mechanism and controls the rate of protein deamination.

3. The parathyroids neutralize certain toxic products of protein decomposition and likewise sensitize the cells of ectodermal origin with the exception of the amyelinic or gray fibers of the nervous system.

4. The suprarenal medulla's secretion neutralizes certain toxic products of protein decomposition and likewise sensitizes the cells of the amyelinic fibers of the nervous system. The action of the two latter glands becomes apparent, as the protein substance is incorporated into the ectodermal cells. They are of the so-called Ehrlich amboceptor type.

5. The thyroid mechanism therefore is directly related to protein metabolism.

6. The hypophysial mechanism consisting of the anterior and posterior lobes of the hypophysis and the suprarenal cortex control the cell development of the mesodermal tissues.

7. The anterior lobe (analogous to the thyroid) is the keystone of the mechanism and controls the amount of carbohydrate and fat metabolism of the blood.

8. The posterior lobe (analogous to parathyroids), through its secretion, sensitizes the cells derived from the mesenchyme. It indirectly influences carbohydrate and fat metabolism by act-

ing as amboceptor for the end products of these as they are incorporated in the cells.

9. The suprarenal cortex (analogous to the suprarenal medulla) sensitizes the cells derived from the mesothelium. It also indirectly influences carbohydrate and fat metabolism by acting as amboceptor for the end products of these metabolisms as they are incorporated in the mesothelial cells.

10. The hypophysial mechanism is under the control of the thyroid mechanism as the hypophysis is an ectodermal tissue. Thyroid disease then gives symptoms in both ectodermal and mesodermal tissues, especially when the thyroid disease persists for any length of time. It likewise influences proteid, carbohydrate and fat metabolisms. It is therefore the most useful of organic extracts.

11. The anterior lobe is sensitized by the parathyroids, the posterior lobe by the suprarenal medulla.

12. The sexual glands are antagonistic to the parathyroids, posterior lobe of the hypophysis, and suprarenal medulla.

13. There is a difference in the antagonizing action of the male and female sexual gland secretion. It is the more active in the female.

14. The medullary portion of the thymus gland is antagonistic to thyroid and hypophysial mechanisms, and therefore holds the sexual glandular function in check.

15. The cortical portion of the thymus has a hematopoietic function and works in conjunction with the posterior lobe on the mesenchymal and mesamœboid tissues of the mesoderma.

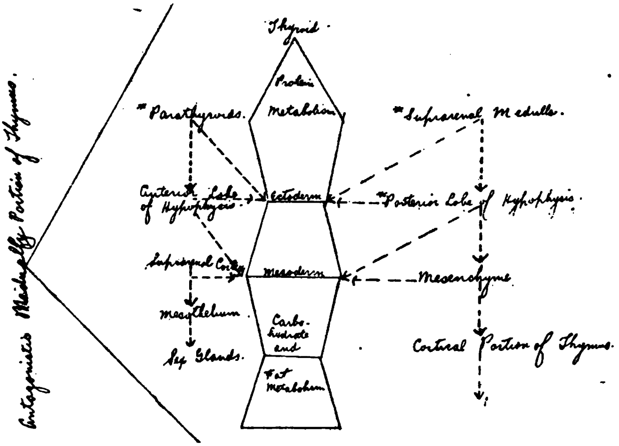
16. The pineal gland function is a speculative one, and no attempt has been made to place it in the category of ductless glands.

In discussing the ductless gland problem as a whole, it becomes very apparent to everyone that the field of thought it opens up is such a broad one that only the more essential points can be touched upon. Quite naturally the individual who advances a hypothesis in this field is led by his enthusiasm to apply it to problems with which the ductless glands have absolutely no relation. It is to the credit of more recent medical science that it has ever erred on the side of conservatism. With all due respect to this conservatism, it is felt that when order has been restored out of the chaotic mass of literature, the relation of the ductless glands to the embryological origin of cells will have found its place. While, it is true that one individual ductless gland is sufficient study for a lifetime, it was deemed advisable to outline a basis for study along embryological lines. The study of one of these ductless glands leads the student into all fields of medicine and thus an elaboration can be carried on "ad infinitum."

It was with this thought of stimulating further research along embryological channels that this article was written, and the ultimate object of applying this, then, to the logical sequence of such reasoning, the problem of tumors. For, if it can be proven beyond question that certain of these individual glands are directly in control of physiological cell growth depending upon their origin, then it would not be unreasonable to suppose that they were related in some way to abnormal cell growth. It must be emphasized, however, that the ductless glands are in no way a direct cause of tumor formation, for the predisposition, whether produced by mechanical, chemical, metabolic or any other form of irritation, must be present. Certain clinical and empirical facts are brought to mind which gave a basis for such reasoning. It is well known and has been emphasized a few years ago that it is when the active sexual life ceases, that tumors are prone to make their appearance. Recall the statement in regard to the sex glands that they are antagonistic to the parathyroids, posterior lobe, and suprarenal medulla, and it seems quite reasonable to suppose that when this antagonistic secretion is lessened or absent, that tumor formation in these controlled tissues is apt to make its appearance under certain favorable conditions. Of course, this does not explain the frequent sarcoma formation in the young, but a detailed discussion of this and other tumor problems would lead to too broad a field for the present article. Suggestive, also, are experiments which have shown that tumor transplants found a more favorable soil in rats which had been fed on a diet affecting the thyroid. Interesting also is the formation of fibroids in women who have never been pregnant. Recall again that the corpus luteum is an antagonistic secretion and that the pregnant woman has a corpus luteum in each pregnancy lasting at least four months. It is therefore more inhibitory and its influence on tissues no doubt is felt for a long period, whereas the nulliparæ, while possessing corpura lutea, have not the lasting inhibitory effect of the corpora lutea vera, of the multiparæ, and therefore under favorable conditions the connective tissue is prone to overgrow in fertile soil. It is especially to be remembered the relation of the hypophysis to the mesodermal tissues, the sex organs, and likewise the lymphocytosis so characteristic of fibroids and the lymphocytosis of pregnancy, labor and the puerperium. Problems of metabolism are also brought to mind whenever ductless glands are discussed. The glycosuric action of thyroid extract, brought about, according to the present hypothesis, through a stimulation of the hypophysis, and likewise the glycosuric action of adrenalin, are interesting phases of these metabolic problems. And so also, as example, the high carbohydrate tolerance of myxedmatous and cretinous individuals showing the opposite phase of the problem. It was endeavored, throughout the article, to tread upon firm ground and draw only those conclusions which the facts at hand would seem to warrant.

In giving the references used in this article, the extensive lists compiled by Falta and Biedl were freely drawn upon and due credit for such must be acknowledged. Whenever possible the references given by these authors were taken direct from their bibliography. As for the other references, they are gathered from various other sources of the voluminous literature.

Below is given a schematic diagram to illustrate the actions and relations of the ductless glands.


Thyroid
Protein Metabolism
*Parathyroids.
*Suprarenal Medulla.
Anterior Lobe of Hypophysis
Ectoderm
*Posterior Lobe of Hypophysis.
Suprarenal Cortex
Mesoderm
Mesenchyme
Mesothelium
Sex Glands.
Carbo-hydrate and Fat Metabolism
Cortical Portion of Thymus.
Antagonistic Medullary Portion of Thymus.

*Those marked with an asterisk are antagonists of the sex glands. Those arrows running horizontally show the embryonic origin while those running vertically show the sensitizing action.

1. Moehlig, R. C. A Study of the Ductless Glands, Detroit M. J., Vol. XIV, 1914.
2. Hitschmann. Augenuntersuchungen bei Kretinismus und Zwergwuchs, etc., Wien. klin. Wchenschr., 1898, Nr. 27.
3. De Schweinitz, G. E. Diseases of the Eye, 1910, p. 348.
4. Falta, W. Ductless Glandular Diseases, 1916, pp. 160, 161.
5. Kocher. Cited by Osler, Modern Med., Vol. VI, 1909, p. 450.

6. Cleveland. Cited by Osler, Modern Med., Vol. VI, 1909.
7. Scholz, W. Über Kretinismus, Ergebn. d. inneren Med. u. Kinderh., 3, 1909 (Falta, 609).
8. Hammerschlag. Cited by Falta, W.
9. Habermann, J. Zur. Lehre der Ohrenerkrankungen infolge von Kretinismus, Arch. f. Ohrenh., Vol. LXXIX, 1909, 23.
10. Alexander, G. Das Gehörorgan der Kretinen. Arch. f. Ohrenh., Vol. LXXVIII, 1908, 54.
11. Danziger. Cited by Ewaldt, Ztschr. f. Path., Vol. II, 1912, 262.
12. Bircher, H. Der endemische Kropf und seine Beziehungen zur Taubstummheit und zum Kretinismus. Basel, 1893.
13. Moos and Steinbrugge. Cited by Ewald, Die Erkrankungen der Schilddrüse, Myxödem und Kretinismus, II. Auff. A. Hölder, Leipzig u. Wien, 1909.
14. Nager. Die Taubstummen der Luzerner Anstalt Hohenrain, Ztschr. f. Ohrenh., Vol. 43, 234.
15. Bircher, E. Ein Beitrag zur Kenntniss der Schilddrüse und Nebenschilddrüse bei Kretinoiden, Kretinen, und endemisch Taubstummen. Frankf. Ztschr. f. Path., Vol. II, 262.
16. Schönemann. Hypophyse und Thyroidea, V. A., Vol. 129, 1892, p. 310.
17. Falta, W. *Ibid.*, pp. 163, 164.
18. Ponfick. Myxödem und Hypophyse. Ztschr. f. klin. Med., Vol. 38, 1899.
19. Boyce and Beadles. Enlargement of the Hypophysis Cerebri in Myxœdema, etc., J. o. P. B., October, 1822, and February, 1893.
20. Rogowitsch. Veränderungen der Hypophysis nach Entfernung der Schilddrüse, Ziegler's Beiträge, Vol. 4, 1889.
21. Brens and Kolisko. Die pathologischen Beckenformen, Leipzig und Wien, 1904 (Deuticke).
22. Scholz, W. Über den Stoffwechsel der Kretinen, Ztschr. f. exper. Path. und Pharmakol., 1905, Nr. 2.
23. Capelle. Ein Neuer Beitrag zum Basedowthymus, Mün. m. W., Vol. 35, 1908.
———. Die Beziehungen der Thymus zum Morbus, Basedowii, Beitr. klin. Chir., Vol. 58, 1908.
24. Möbius, P. J. Die Basedowsche Krankheit, Wien, 1906, Holder.

25. Bordley. Malignant Uveitis Treated with Thyroid Extract, J. A. M. A., Vol. 67, August, p. 412, 1916.

26. Osler. Modern Medicine, Vol. 6, p. 433, 1909.

27. Holmgren, J. Über das Längenwachstum bei Hyperthyriose, Med. Klin., 1910. Über den Einfluss der Basedowschen Krankheit, etc., auf das Längenwachstum, Leipzig, 1909.

28. Ballet. Gigantisme et gôitre exophthalmique, Arch. de Neurol., Vol. 19, 1905.

29. Falta, W. *Ibid,* p. 79, 1916.

30. Notkin. Beitrag zur Schilddrüsenphysiologie, Wien. Med. Wochenschr., 1896, u. Vir. Arch., Vol. 144, Suppl.

31. Blum, F. Die Schilddrüse als entgiftendes Organ, Berl. klin. Wochenschr., 1898.
———. Die Schilddrüse als entgiftendes Organ, Virch. Arch., Vol. 162, p. 375, 1900.

32. Biedl. Innere Sekretion, p. 103, 1910, Berlin.

33. Hunt, R. Influence of Thyroid Feeding and of Various Foods and of Small Amounts of Food upon Poisoning by Aceto-Nitril, Proc. Soc. Exp. Biol., New York, Oct. 18, 1905, J. Biol. Chem., Vol I, p. 33, October, 1905.

34. Lorand, A. Old Age Deferred, F. A. Davis Co., Phila., p. 141, 1914.

35. Biedl. Innere Sekretion, p, 104, 1910, Berlin.

36. Perrin M. et Jeandelize, P. Moindre résistence des lapins thyroidectomisés à l'intoxication par le chlorure mercurique, Comp. rend. de la soc. de biol., Vol. 67, pp. 849, 851, 1909.

37. Breisacher, Leo. Unters. über die gland. thry., Archiv. f. Anat. und Physiol. Suppl., p. 509, 1890.
———. The Clinical Application of Some Thyroid Gland Experiments, J. A. M. A., 1903.

38. Kishi. Beiträge zur Physiologie der Schilddrüse, Vir. Arch., Vol. 176, 1904.

39. Kendall, E. C. The Function of the Thyroid—Parathyroid Apparatus, J. A. M. A., Vol. 66, March, pp. 811-813, 1916.

40. Vaughan, V. C. The Phenomena of Infection, J. A. M. A., Vol. 52, pp. 585-589, 1914.

41. Vassale, G., et Generali. Sur les effets de l'exstirpation des glandes parathyroides, Arch. ital. de Biol., Vol. 25, p. 459, Vol. 26, p. 61, 1896, and Vol. 33, 1906.

42. Pfeiffer, H., and Mayer, O. Exper. Beitr. z. Kenntnis d. Epithelkörperchenfunction, Wien. K. Wochenschr., 1907.

43. Biedl. Innere Sekretion, p. 56, 1910, Berlin.

44. Ceni L'Besta. Proprietà terapeutiche specifiche del siero di sangue di animali immunizzati con siero di animali stiroparatiroidiati, Riv. Sper. di Freniatria, 1903.

45. Gley, E. Des effects de l'extirpation des glandules parathyroides chez le chien et le lopin, Arch. de Physiol. normal et pathol., p. 18, 1897.

46. Ughetti. Cited by Biedl., p. 56, 1910.

47. Canizzaro. Über die Funktion der Schilddrüse, Deut. med. Wochenschr., 1892.

48. Berkeley and Beebe. Extract of Parathyroids, J. Med. Res., February, 1909.

49. Frouin, A. Sur la possibilité de conserver les animaux après l'ablation complète de l'appareil thyroidien, en ajoutant des sels de calcium eu de magnésium à leur nourriture, Compt. rend. de l'acad. des sciences, Vol. 148, p. 1622, 1908.

50. Kendall, E. C. The Function of the Thyroid-Parathyroid Apparatus, J. A. M. A., Vol. 66, March, pp. 811-813, 1916.

51. Koch, W. F. Physiology of Parathyroid Glands, J. Lab. and Clin. Med., Feb. 1, No. 5, 1916.

52. MacCallum, W. G. On the Production of Specific Cytolic Sera for Thyroid and Parathyroid, with Observations on the Physiology and Pathology of the Parathyroid Gland, Especially in Its Relation to Exophthalmic Goiter, Med. News, Oct. 31, 1903.

————. Die Beziehung der Parathyroiddrüsen zu Tetanie, Centralbl. f. Allgem. Pathol. und Pathol. Anat., Vol. 76, 1905.

53. Ochsner, A. J. Thyroid and Parathyroid Glands, p. 335, 1910.

54. Schwarz, O. Über einige Anfallerscheinungen nach Extirpation beider Nebennieren, Wien. Klin. Wochenschr., 1909.

55. Brown-Séquard. Influence heureuse de la transfusion du sang normal après l'extirpation des capsules surrénales chez le cobaye, Comptes rend. de la soc. de biol., p. 467, May 14, 1893.

56. Marioni, F. Ricerche sperimentali sulla funzione delle capsule surrenali, Clin. med. Ital., 1906.

57. Soddu, L. Intorno agli effetti della estirpazione delle capsule surrenali nel cane Sperimentale, 52, Ref. Centralb. f. innnere Med., Vol. 20, 1899.

58. Charrin et Langlois. Lésiones des caps surrén. dans l'infection. Comptes rend. de la soc. de biol., p. 410, 1894.

59. Strümpell, A. Text Book of Medicine, Vol. II, pp. 612-614, 1912.

60. Jaksch, V. Klinische Beiträge zur Tetanie, Ztschr. f. klin. Med., 1890.

61. Frankl-Hochwart, F. Die Tetanie der Erwachsenen, Wien, 1891; 2. Aufl., 1907.

———. Die Prognose der Tetanie der Erwachsenen, Neurol. Centralbl., Vols. 14, 15, 1906.

———. Die Schicksale der Tetaniekranken, Wien. Med. Wochenschr., 1906.

62. Falta, W. *Ibid.*, p. 196, 1916.

63. Adler, S., und Thaler, H. Experimentelle und klinische Studien zur Graviditatstetanie, Ztschr. f. Geburtsh. u. Gynaek., Bd. 62, 194, 1909.

———. Diskussion zum Vortrag-Erdheim, Wien. klin. Wochenschr., 1906.

64. Walbaum, Unters. Über die Epithelkörperchen beim Kaninchen-Mitteil aus den Grenz. der Med. und Chir., Bd. 12, 1903.

65. Spiegler. Protokol. Gesellsch. d. Aerzte, Wien. klin. Wochenschr., Bd. 357, 1909.

66. Peters, A. Tetanie und Starbildung, Bonn, 1898.

———. Weitere Beitrage über Tetanie und Starbildung, Ztschr. f. Augenh., Bd. 5, p. 89, 1901; see also Pathologie der Linse Lubarsch-Ostertag. Ergebnisse, Morp. u. Path. der Sinnesorgane, p. 502, 1906.

67. Erdheim, J. Morphologische Studien über die Beziehung der Epithelkörperchen zum Kalkstoffwechsel, V. Frankf. Ztschr. f. Pathol., Bd. 7, p. 295, 1911.

68. Falta, W. *Ibid.*, pp. 198, 199, 1916.

69. Strümpell, A. Text Book of Medicine, Vol. II, pp. 193-195, 1912.

70. Ochsner, A. J. Thyroid and Parathyroid Glands, p. 291, 1910.

71. Gray's Anatomy, p. 824, 17th Ed., 1908.

72. *Ibid.*, p. 1079, 17th Ed., 1908.

73. ZIEGLER. Text Book of Pathology, 1910.

74. CZERNY, A. Hydrocephalus und Hypoplasie der Nebennieren, Centralbl. f. Allg. Path., Bd. 10, 281, 1899.

75. HANSEMANN, D. V. Über Anaplasie, Spezifizität und Altruismus der Zellen, Berlin, 1891.

76. WIESEL, J. Zur pathologischen Anatomie der Addisonschen Krankheit, Ztschr. f. Heilk., Bd. 24, 1903.
————. Hemicephalie, Mitt. d. Gesellsch. f. innere Med., Wien, Bd. 144, 1907.

77. KAUFMANN, E. Spezielle Pathologische Anatomie, p. 772, 1909, 5. Auflage.

78. GRAY'S ANATOMY, p. 871, 1908.

79. *Ibid.*, p. 914, 1908.

80. *Ibid.*, p. 872, 1908.

81. *Ibid.*, pp. 886-910, 1908.

82. HOSKINS, R. G. The Practical Significance of the Adrenals, J. A. M. A., Vol. 62, p. 1803-1805, 1914.

83. OSLER. Modern Medicine, p. 366, Vol. 6, 1909.

84. ADAMI. Principles of Pathology, Vol. 1, p. 893, 1908.

85. FALTA, W. *Ibid.*, p. 342, 1916.

86. GRAY'S ANATOMY, p. 833, 1908.

87. *Ibid.*, p. 822, 1908.

88. *Ibid.*, p. 908, 1908.

89. CRILE, G. The Origin and Nature of the Emotions, W. Saunders, Phila., 1915.

90. MAYO, C. Collected Papers of Mayo Clinic, 1916, W. B. Saunders, Phila.

91. CRILE, G. The Kinetic Drive, J. A. M. A., Vol. 65, December, 1915, p. 2129.

92. STRAUB, W. Mechanismus der Adrenalinwirkung und die mögliche Bedeutung der Substanz für den Kreislauf, Münch. med. Wochenschr., 1907.

93. KRETSCHMER, W. Über den Mechanismus der Adrenalinwirkung und dauernde Blutdrucksteigerung durch Adrenalin, Arichiv f. Exper. Path. und Pharm., Bd. 57, p. 348, 1907.

94. GRAY'S ANATOMY, p. 917, 1908.

95. KAUFMANN, E. Spezielle Pathologische Anatomie, p. 1135, 1909, 5. Aufl.,

96. WATANABE and CRAWFORD. Abst. J. A. M. A., Vol. 46, February, p. 604, 1916.

97. Strümpell, A. Text Book of Internal Medicine, Vol. 2, 1916.

98. Gray's Anatomy, p. 959, 1908.

99. *Ibid.*, p. 958, 1908.

100. McHarrison. J. A. M. A., Abst., Mar. 7, 1914.

101. Sabourin. Zeitschr. f. Physiol. Chem., LXXXVII, 1913.

102. Biolokur. J. A. M. A., Abst., Vol. 45, October, p. 1412, 1915.

103. Pottenger. The Syndrome of Toxemia, etc., J. A. M. A., Vol. 56, January, 1916.

104. Strümepll, A. Text Book of Medicine, Vol. 1, p. 422, 1912.

105. Trauter and Rowe. The Refractometric Determination of Albumin, etc., J. A. M. A., Vol. 65, p. 1433, 1915.

106. Beeson, Chas. The Thyroid Gland in Relation to Pellagra, J. A. M. A., Vol. 63, p. 2129, December, 1914.

107. Morse, Plinn F. J. Lab. and Clin. Med., Vol. 1, No. 4.

109. Roux and Yersin. Cited by Falta, p. 341, 1916.

110. Charrin et Langlois. Lésiones des caps surrén. dans l'infection, Compt. rend. de la soc. de biol., p. 812, 1893.
———. Hypertrophie expérimentale des capsules surrenales, *Ibid.*, p. 131, 1896.

111. Pettit, A. De l'action de quelques substances toxiques sur la glande surrénale, Bull. d. Mus., Nr. 4, 1896.

112. Bogomolez, A. Zur Frage über die Veränderungen der Nebennieren bei experimenteller Diphtherie, Ziegler's Beitr., Bd. 38, p. 510, 1905.

113. Tarchanow. Über einige physiologische Wirkungen des Adrenalins auf Tiere, Russki Vratsch., Nr. 47, 1902, Ref. Biochem. Centralbl., Bd. 1, p. 369, 1903.

114. Labzine, M. M. De la régénération des glandes surrénales, Arch. Science Biol., Bd. 11, p. 319, 1905.
———. Thèse de St. Pétersbourg, 1904.

115. Luksch, F. Funktionsstörungen der Nebenniere bei Allgemeinerkrankungen, Intoxikationen und Infektionen, Wien. klin. Wchenschr., 1905.
———. Über die Störung der Nebennierenfunktion bei Infektionskrankheiten, Berl. klin. Wchenschr., 1909.

116. SCHUR, H., und WIESEL. Über eine der Adranalinwirkung analoge Wirkung des Blutserums von Nephritikern auf das Froschauge, Wien. klin. Wchenschr., Nr. 23, u. 27, 1907.

———. Zur Frage d. drucksteigernden Subst. im Blute bei Chron. Nephritis, Deut. m. Wchenschr., 1907.

117. GOLDZIEHER und MOLNAR. Beiträge zur Frage der Adrenalinämie, Wien. klin. Wchenschr., 1908.

———. Pathologie der Nebennieren, Orvosi Helilap, Nr. 16, 1908.

118. CUSHING, H. The Pituitary Body and Its Disorders, J. B. Lippincott, Philadelphia, 1910.

119. BIEDL. Innere Sekretion, Berlin, 1910.

120. DELILLE, A. L'hypophyse et la modification hypophysaire, Paris, 1909.

121. SOLOMON, H. Über den Diabetes innocens der Jugendlichen, etc., Deutsch. med. Wchenschr., Vol. 60, January, 1913, p. 2.

122. FALTA, W. *Ibid.*, p. 259, 1916.

123. *Ibid.*, p. 248, 1916.

124. *Ibid.*, p. 260, 1916.

125. GOETSCH, CUSHING and JACOBSON. Carbohydrate Tolerance and the Posterior Lobe of the Hypophysis Cerebri, Johns Hopkins Hospt. Bulletin, Vol. 22, June, 1911.

126. FORCHHEIMER. Therapeusis of Internal Diseases, Vol. 1, p. 89, 1915.

127. BIERRY and MALLOISEL. Comp. rend. Soc. Biol., LXV, 232, 1908.

128. PARGES. Zeit. f. klin. Med., LXIX, 341, 1909.

129. CROFTAN. Uber das diastatische Ferment der Nebennieren, Pflüger's Arch., Bd. 90, 1902.

130. GUERRINI, G. Sur les fines modifications de structure de quelques organes dans le cours de la fatigue (foie, rein, hypophyse, capsules surrenales). Arch. Ital. de Biol., Vol. 49, pp. 161-170, 1908.

131. MARINO-ZUCCO, F. and L. Untersuchungen über die Addisonsche Krankheit, Moleschotts Unter. zur Natur., Bd. 14, pp. 59-63, 1892; Ital. Ref. Med., VIII, 64, 1892.

132. BIEDL. Innere Sekretion, Berlin, p. 254, 1910.

133. Kölliker, V. Handbuch der Gewebelehre des Menschen. a Aufl., 1855; 3. Aufl., 1859; 4. Aufl., 1863; 5. Aufl., 1867.
————. Entwicklungsgeschichte des Menschen und der höheren Tiere, 2 Aufl., 1879.

134. Forchheimer. Therapeusis of Internal Diseases, Vol. VI, 1915.

135. Biedl. Innere Sekretion, Berlin, p. 268, 1910.

136. Eppinger, Falta and Rudinger. Wechselwirkung der Drüsen mit innerer Sekretion, I u. II, Ztschr. f. klin. Med., Bd. 66 u. 67.

137. Novak, J. Inhibitory Influence on Genital Sphere of Loss of Adrenals, Abst. J. A. M. A., Vol. 62, January, 1914, p. 243.

138. Biedl. Innere Sekretion, pp. 270-278, 1910.

139. Hoskins, R. G. The Practical Significance of the Adrenals, J. A. M. A., pp. 1803-1805, Vol. 62, 1914.

140. Kyrle. Verhandl. d. physiol. u. morph. Gesellsch., Wien, Bd. 5, p. 4, 1904.

141. Osler. Modern Medicine, Vol. VI, p. 364, 1909.

142. Falta, W. *Ibid.,* p. 356, 1916.

143. Falta, W. *Ibid.,* p. 235, 1916.

144. Kaufmann, E. Speziele Pathologische Anatomie, p. 772, 5. Aufl., 1909.

145. Lannois, Pinard and Gallais. Cited by Falta, p. 360.

146. Bullock and Sequeira. Trans. Path. Soc., LVI, 189, 1905.

147. Glynn. The Adrenal Cortex, Its Rests and Tumors, Its Relation to Other Ductless Glands and Especially to Sex, Quart. J. of Med., Vol. 5, p. 157, January, 1912.

148. Marchand. Beiträge zur norm u. path. Anat. d. Gland. carot. u. der Nebennieren, Festschr. f. Virchow, 1891, 557.

149. Guieyesse. La capsule surrénale du cobaye, J. de l'anat. et de la physiol., Bd. 37, pp. 312, 435, 1901.

150. Stoerk, zur Histogenese der Grawitzschen Nierengeschwülste. Beitr. z. path. Anat. u. Physiol., Bd. 43, p. 383.

151. v. Haberer and Stoerk. Beitrag zur Marksekretion der 1908.
Nebenniere, Wien. klin. Wchenschr., 305 u. 308, 1908.

152. Falta, W. *Ibid.,* pp. 362, 363, 1916.

153. Rolleston, H. D. Note on the Anatomy of the Suprarenal Bodies, J. of Anat. and Physiol., Vol. 26, 1892.
———. The Goulstonian Lectures on the Suprarenal Bodies, Brit. Med. Journ., p. 629, Bd. 745, 687.
———. Some Problems in Connection with the Suprarenals, Lancet, 1907.

154. Molon, C. Sulla glicosuria adrenalinica, Gazz. d. Osped., 1908.

155. Fischer, B. Hypophyse, Akromegalie und Fettsucht, Wiesbaden, Bergmann, 1910.

156. Delille, A. L'hypophyse et la médication d'hypophyse, Paris, 1909.

157. Schultze, F., and Fischer, B. Zur Lehre von der Akromegalie und Osteoarthropathie hypertrophiante, Mitt. a. d. Grenzgeb., Deutsch. Med. und Chir., Bd. 24, 607, 1912.

158. Schur, H., und Wiesel, J. Zur Frage d. drucksteigernden Subst. im Blute bei chron. Nephritis, Deutsche med. Wchenschr., 1907.

159. V. Noorden. Cited by Falta, p. 264. Über neurogenen Diabetes, Med. Klin., 1912, Nr. 1.

160. Falta, W. *Ibid.*, p. 193, 1916.

161. *Ibid.*, p. 194.

162. v. Moraczewski. Stoffwechsel bei Akromegalie, etc., Ztschr. f. klin. Med., Bd. 43, 336, 1901.

163. MacCallum and Voegtlin. On the Relation of Tetany to Parathyroid Glands and to Calcium Metabolism, J. Exper. Med., Vol. 11, 1909.

164. Morel. Les parathyröides dans l'ostéogenèse, Compt. rend. soc. de biol., Vol. 68, 163, 1910.

165. Canal. Augm. influenza della parthyroidei sul decorso di guariguone delle fratture, Arch. per le sc. Med., Vol. 4, 1910.

166. Leopold and 1. Reuss. Über die Beziehungen der Epithelkörperchen zum Kalkbestand des Organismus, Wien. klin. Wchenschr., 1343, 1908.

167. Schüller. Rachitis tarda und Tetanie, Wien. med. Wchenschr., 1909.

168. Falta. *Ibid.*, p. 196.

169. Falta and Kahn. Studien über Tetanie, etc., Ztschr. f. Klin. Med., Bd. 72, 1911.

170. J. A. M. A., Editorial, Dec. 14, 1913.

171. Falta. *Ibid.*, 253.

172. HALBAN. Zur Lehre von der Menstruation, etc., Centralbl. f. Gynäk., Bd. 35, 46, 1911.

173. FRANKEL. Berl. klin. Wchenschr., Nr. 2, 1911.

174. MCCORD, C. Occurrence of Pituitary Extract and Epinephrin in Fetal Pituitary and Suprarenal Glands, Jn. Biol. Chem., Vol. 33, pp. 413, 527, December, 1915.

175. BAER, J. L. The Leucocytes in Pregnancy, Labor and the Puerperium, Surg. Gynec. and Obst., p. 567, Vol. XXIII, 1916.

176. EDGAR. Practice of Obstetrics, p. 709, 1916.

177. FALTA. *Ibid.*, p. 383.

178. MÖBIUS, P. J. Die Basedowsche Krankheit, Wien., 1906.

179. KRABBEL. Beitr. z. Klin. Chir., LXXIII, 193, 1911.

180. FALTA. *Ibid.*, p. 363.

181. SABOURAND, R. J. Connection between Genital Development and Pathology of the Hair, Archiv. Mensuell. d'Obstet. et d. Gyn. Jour., 111, 1914.

182. MAGNUS-LEVY. Der Einfluss von Krankheiten auf den Energiehaushalt im Ruhestand, Ztschr. f. klin. Med., Bd. 60, 1906.

183. SOLOMON, H. Gaswechsel bei Morbus Basedowii und Akromegalie, Berl. klin. Wchenschr., Nr. 24, 1904.

184. FALTA. *Ibid.*, p. 388, 1916.

185. CHERAN. Cited by Biedl, Innere Sekretion, p. 326, 1910.

186. VIRCHOW. *Ibid.*

187. BASCH. Die Beziehung der Thymus zum Nervensystem, Jahrb. f. Kinderh., 58, 1908.

———. Beiträge zur Physiologie und Pathologie der Thymus, Jahrb. f. Kinderh., 64, 1906.

188. HART and NORDMANN. Experimentelle Studien über die Bedeutung der Thymus, etc., Berl. klin. Wchenschr., 814, 1910.

189. KLOSE and VOGT. Klinik und Biologie der Thymusdrüse, Tübingen, 1910.

190. PATON. The Relationship of the Thymus to the Sexual Organs, J. of Physiol., Vol. 32, 1904.

191. BARTEL, J. Über die hypoplastiche Konstitution und ihre Bedeutung, Wien. klin. Wchenschr., Nr. 22, 1908.

192. HERMANN and KYRLE. Verhandl. d. phys. u. morp. Gesellsch. Wien., Bd. 5, 4, 1909.

193. Hammar, A. Zur Histogenese und Involution der Thymus, Anat. anz., 1905.

———. Zur grösseren Morphologie und Morphogenie der Menschenthymus, Anat. Hefte., Bd. 43, p. 203, 1911.

———. 50 Jahre. Thymusforschung, Kritische Übersicht der Normalen Morphologie, Ergebn. d. Anat. u. Entwicklungsgesch., Bd. 19, 1, 1910.

194. Maximow. Untersuchungen über Blut und Bindgewebe.

———. II Über die Histogenese der Thymus bei Säugetieren, Arch. f. Mikr. Anat., Bd. 7 u. 14, 1909.

195. His. Über den Sinus praecervicalis und über die Thymusanlage, Arch. f. Anat. u. Physiol., 1886, Anat. Abt., 421.

196. Stieda. Untersuchungen über die Entwicklung der Glandula thymus, Leipzig, 1881.

197. Hansemann. Cited by Lewis, Keibel and Ball's Embryology, 1912.

198. Falta. *Ibid.*, 223.

199 Pappenheimer. Symposium on Internal Secretions in Relation to Gynecology, Transactions of Amer. Gynecol. Soc., June 1, 1917.

200. Soli, U. Les testicules chez les animaux ayant subi l'ablation de thymus, Presse médicale., 1907.

———. Comment se comportent les testicules chez les animaux privés de thymus, Arch. ital. d. Biol., 47, 1907.

201. Klose and Vogt. Beitr. zur. klin. Chir., LXIX, 1, 1910.

202. Hewer. Thymus and Reproductive Organs, etc., J. of Physiol., Vol. 1, p. 638, 1916.

203. Fulci. Transactions of Amer. Gynecol. Soc., June 1, 1917, Symposium on Internal Secretions in Relation to Gynecology.

204. Bomprani. *Ibid.*

205. Henderson. Journ. of Physiol., XXXI, 221, 1904.

206. Paton. *Ibid.*, XLII, 267, 1911.

207. Hammar. Cited by Keibal and Ball, Human Embryology, 1912.

208. Über die Natur der Thymuselemente, Anat. Hefte., Bd. 31, 409, 1906.

209. Sabrozes and Bonnes. Examins. du sang dans l'akromegalie, Compt. rend. soc. de biol., Bd. 57, 1905.

210. Messedaglia. Studio sulla akromegalia, Padova, 1908.

211. Roth. Beitrag zur Symptomenlehre der Geschwülste der Hypophyse cerebri, Arch. f. Opth., Bd. 34, p. 81.

212. Exner. Beiträge zur Pathologie und Pathogenese der Akromegalie, Mitt. a. d. Grenzgeb. d. Med. u. Chir., Bd. 20, 1909.

213. Falta. *Ibid.*, p. 34.

214. Sommer, A., and Florcken, H. Uber die Funktion der Thymus, Sitzungsber. d. physiol. med. Gesell. z. Würzburg., 45, 1908.

215. Basch, K. Uber die Beziehung der Thymus zum Nervensystem, Jarhrb. f. Kinderh., Bd. 58, 1908.

216. Sabatani. Cited by Biedl, Innere Sekretion, 1910.

217. Biedl. Innere Sekretion, 1910.

218. Morowitz. Cited by Falta, *Ibid.*, p. 427.

219. Tandler, J. Über den Einfluss der innersekretorischen Anteile der Geschlechtsdrüsen auf die äussere Erscheinung des Menschen, Wien. klin. Wchenschr., Bd., 459, 1910.

220. Noorden, V. Über chlorose, Med. Klin., Nr. 1, 1910.

221. Hastings, Gilford. The Disorders of Postnatal Growth and Development, London, Adlard and Son, 1911; also Med. Chir. Tr., Vol. 80, 1897, and Practitioner, Vol. 73, p. 188, 1904.

222. Falta. *Ibid.*, p. 432.

223. Virchow. Cited by Anders, Practice of Medicine, p. 461, 1911.

224. Falta. *Ibid.*, p. 468.

225. Massalongo, R. Hyperfunktion der Hypophyse, Riesenwuchs, und Akromegalie, Centralbl. f. Nervenh. u. Psychiat., Bd. 281, 1895.

226. Brissaud. Leçons sur les malad. nerv. (Hôp. St. Antoine), Paris, 1899.

227. Meige, H. Sur le Gigantisme, Arch. gén. de Méd., October, 410, 1902.

228. Ogle, C. Sarcoma of Pineal Body, Tr. Path. Soc., London, Vol. 1, p. 4, 1899.

229. V. Frankl-Hochwart. Zur Diagnose der Zirbeldrüsentumoren, Deutsch. Ztschr. f. Nervenh., Bd. 37, 1909.

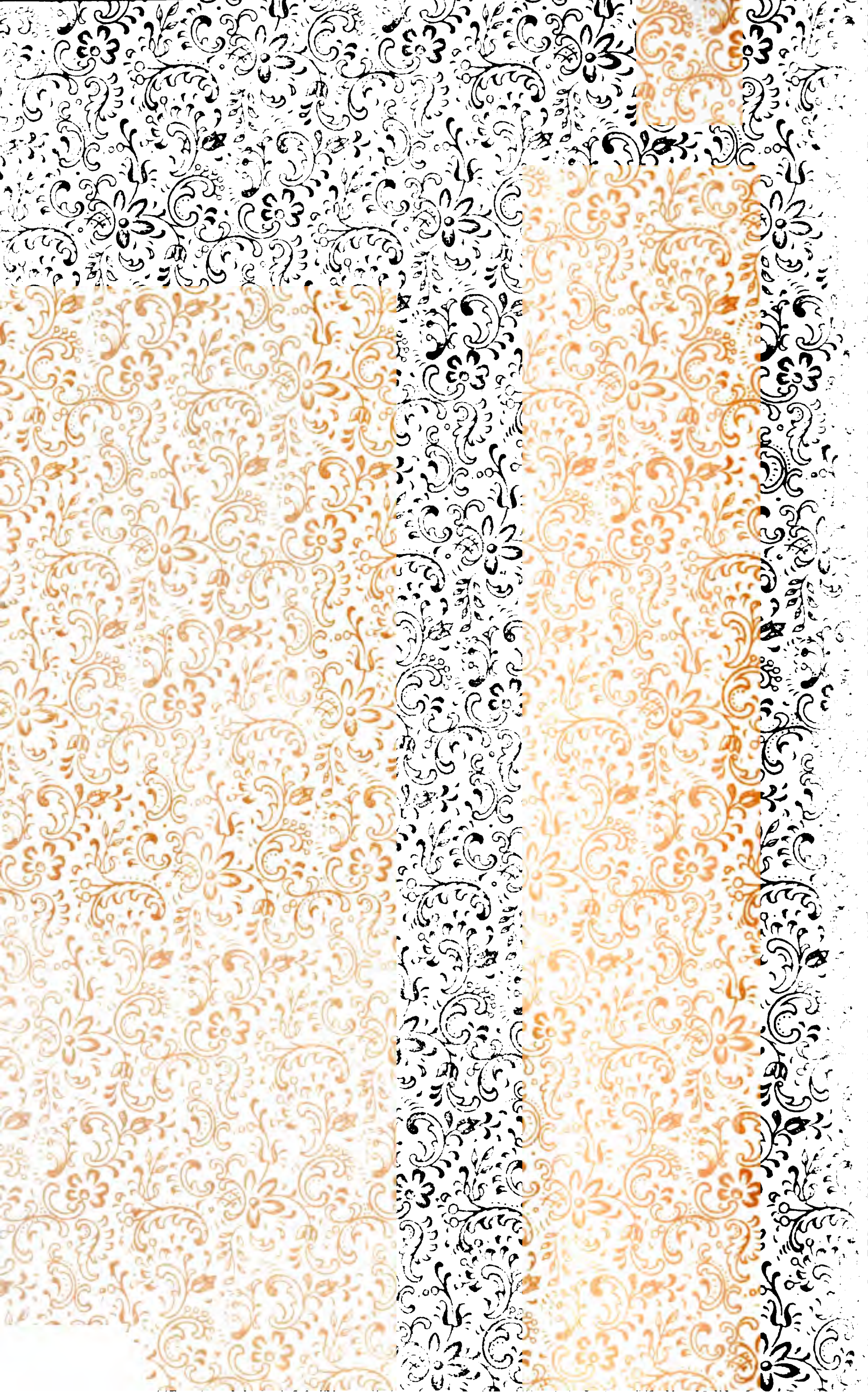
230. McCord, C. The Pineal Gland in Relation to Somatic, Sexual and Mental Development, J. A. M. A., Vol. 63, p. 232, July, 1914.

231. Marburg, O. Die Adipositas cerebralis, etc., Deutsch. med. Wchenschr., 2009, 1908.
————. Deutsch. Ztschr. f. Nervenh., Bd. 36, 1909, u. Wien. med. Wchenschr., 2512, 1907.
————. Die Epiphyse, Ergebn. d. Nerol. Springer, 1912.

232. Raymond and Claude. Les tumeurs de la glande pinéale chez l'enfant, Bull. Acad. de méd., 15 Mars, 1910.

233. Jordan, H. E. The Histogenesis of the Pineal Body of the Sheep, Am. J. Anat., Vol. XII, pp. 249-270, 1911-1912.

Robert C. Moehlig, M.D., 1st Lieut. M.R.C.
1037 Van Dyke Ave., Detroit, Mich.



COUNTWAY LIBRARY
HC 28P7 S